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Synthesis of difluorinated pseudopeptides using chiral α,α-difluoro-β-amino acids in the Ugi reaction

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In memory of Miss Anne-Laure Janer who passed away in January 2003

Abstract—2,2-Difluoro-3-(2-hydroxy-1 *R*-phenylethylamino)-3 *S*-phenylpropionic acid **3**, obtained by a Reformatsky-type reaction of ethyl bromodifluoroacetate with (4*R*)-2,4-diphenyloxazolidine, was used as a classical carboxylic acid in the Ugi reaction to prepare various difluorinated pseudopeptides **5a**–**n**. Compounds **5** were then deprotected by hydrogenolysis to furnish difluorinated pseudopeptides **6**.

Multicomponent condensation (MCC) reactions and in particular the Ugi four-component coupling reaction,[1] have recently appeared as efficient methods for the synthesis of diverse libraries of small molecules such as benzodiazepines, lactams, pyrroles, *C*-glycoside peptide ligands and diketopiperazines.[2] As a synthetic tool for creating diverse compound libraries, the Ugi reaction accepts a wide range of components although the range of available isocyanides is limited. To overcome the limited commercial availability of isocyanides, several new isocyanides have been recently introduced.[3]

Furthermore, fluoro compounds have raised a great deal of interest. Indeed, the presence of a fluorine atom introduces modifications to the physiological activity of bioactive compounds.[4] In particular *gem*-difluoro amino acids and derivatives have been the subject of an important area of research as the CH_2/CF_2 transposition has been recognized as a valuable tool in the blockage of metabolic processes. Replacement of various functional groups by a *gem*-difluoromethylene moiety has generated potent transition-state-type inhibitors.[5] Additionally, β-amino acids are now recognized as valuable tools for the generation of new derivatives[6] such as β-peptides[7] as well as building blocks for β-lactam antibiotics.[8] We have recently described[9] the enantioselective synthesis of α,α-difluoro-β-amino acids via the Reformatsky-type reaction of ethyl bromodifluoroacetate with chiral 1,3-oxazolidines (Scheme 1).

This article describes the application of these α,α-difluoro-β-amino acids in the Ugi reaction. Due to the bifunctionality encountered in the α,α-difluoro-β-amino acids **4**, subsequent transformations of these compounds were necessary to block either the amine or carboxylic acid terminus before their use in the Ugi reaction to avoid the formation of lactams. We decided to block the amine function in order to use the highly reactive carboxyl terminus in the Ugi reaction. Several protecting groups were tested such as Boc, Cbz, Ses and tosyl. In the case of the Boc protection, we observed a very low yield and rapid deprotection because of the intrinsic acidity of the α,α-difluoro-β-amino acid. For Ses and Cbz, very low yields were again obtained. Tosyl protection was efficiently realized (50%) but its removal requires drastic conditions, which are not compatible with peptide bonds. Finally we decided to test compound **3** directly in the Ugi reaction and used the chiral auxiliary as a nitrogen protecting group, even though it contains a hydroxyl moiety and does not eliminate the reactivity of that secondary nitrogen. In a first attempt,[10] methanolic solutions of benzylamine, benzaldehyde, commercially available ethyl isocyanoacetate and compound **3** were mixed at room temperature for

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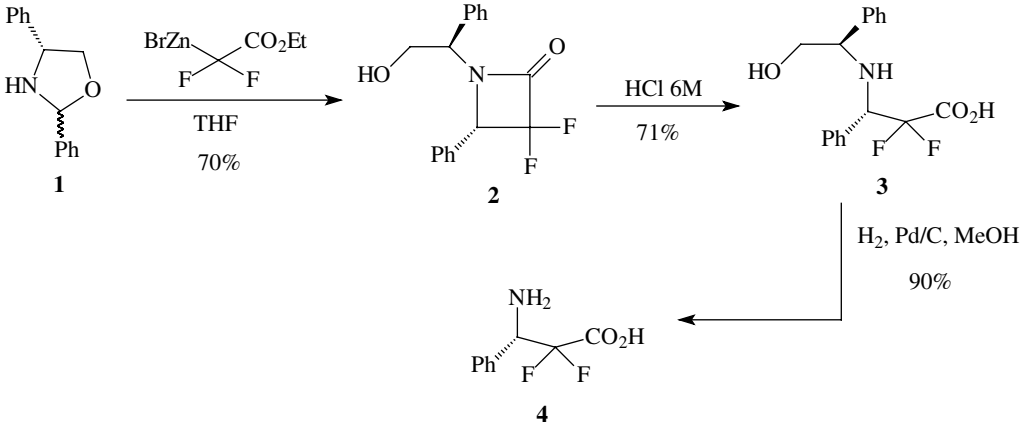
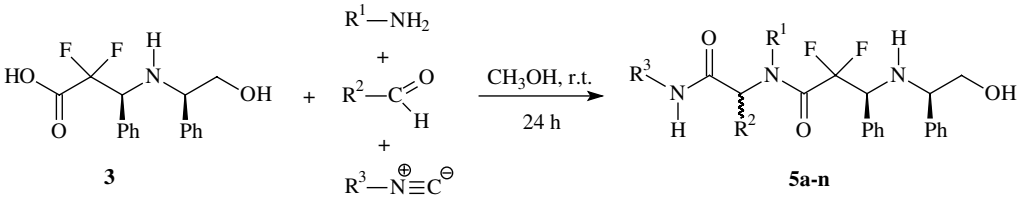


Scheme 1.



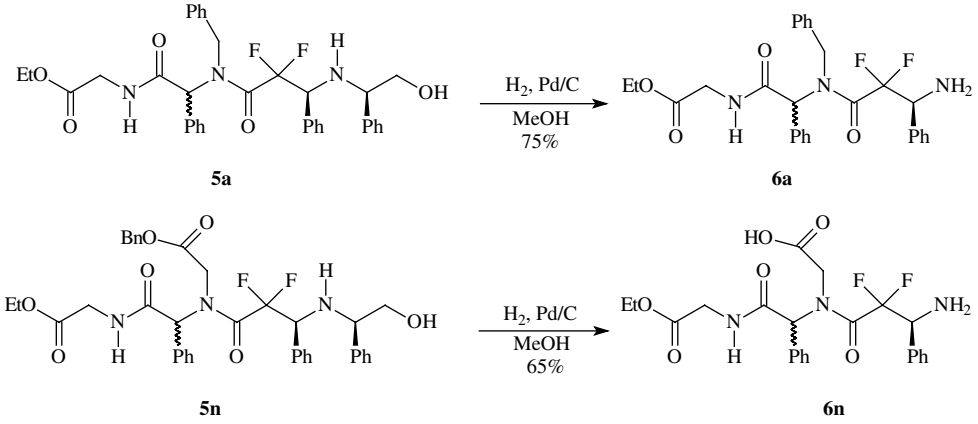
Scheme 2.

Table 1. Synthesis of difluorinated pseudopeptides **5a–n**

Compound	R^1	R^2	R^3	Yield (%)
5a	Ph–CH_2	Ph	$EtOC(O)CH_2$	95
5b	Ph–CH_2	CH_3–$(CH_2)_4$	$EtOC(O)CH_2$	73
5c	Ph–CH_2	*trans*-Ph–CH=CH	$EtOC(O)CH_2$	63
5d	Ph–CH_2	4-Pyridyl	$EtOC(O)CH_2$	55
5e	Ph	Ph	$EtOC(O)CH_2$	68
5f	Ph	CH_3–$(CH_2)_4$	$EtOC(O)CH_2$	40
5g	Ph	*trans*-Ph–CH=CH	$EtOC(O)CH_2$	61
5h	Ph	4-Pyridyl	$EtOC(O)CH_2$	81
5i	Ph–CH_2	Ph	2-TBSO-C_6H_4	67
5j	Ph–CH_2	CH_3–$(CH_2)_4$	2-TBSO-C_6H_4	57
5k	Ph–CH_2	*trans*-Ph–CH=CH	2-TBSO-C_6H_4	50
5l	Ph–CH_2	4-Pyridyl	2-TBSO-C_6H_4	54
5m	2-BocNH–C_6H_4	Ph	2-TBSO-C_6H_4	34
5n	$BnOC(O)CH_2$	Ph	$C_2H_5OC(O)CH_2$	46

24 h leading to difluoro pseudopeptide **5a** in 95% yield. As previously noted, no diastereoselectivity was observed. Indeed, in early work, Bock and Ugi[11] determined that use of a chiral acid or isonitrile in the Ugi MCC reaction did not provide any degree of diastereoselectivity. We then applied this methodology by changing each of the three components in the Ugi reaction in order to generate a small library of difluorinated pseudopeptides (Scheme 2). For the amine component, we used benzylamine, aniline, *O*-benzylated glycine and *N*-Boc-phenylenediamine; benzaldehyde, hexanal, 4-pyridylcarboxaldehyde and *trans*-cinnamaldehyde were used as the aldehyde source. For the isonitrile component, we used ethyl isocyanoacetate and the isonitrile developed by Linderman et al.[3c] Finally, for compound **3**, (*R*)-phenylglycinol was used in each case as chiral auxiliary. All the results obtained for the generation of this small library are collected in Table 1.

In most cases, the Ugi reaction occurred smoothly, affording difluorinated pseudopeptides **5** with satisfactory yields of the purified product. In most cases, diastereoisomers were easily separated by column chromatography on silica gel. We then turned our attention towards the removal of (*R*)-phenylglycinol (Scheme 3). In the case of **5a**, hydrogenolysis of the



Scheme 3.

nitrogen appendage cleaved the phenylglycinol part selectively (75% yield) furnishing **6a** without elimination of fluorine. In the case of **5n**, hydrogenolysis cleaved the phenylglycinol part and the benzylic ester (65% yield) leading to **6n**.

In conclusion, we have performed the Ugi reaction using an α,α-difluorocarboxylic acid leading to difluorinated pseudopeptides in moderate to high yields. Further investigations, especially solid-phase applications, removal of the isonitrile moiety (using the 'convertible' isonitrile), post-condensation and cyclization leading to heterocyclic rings (e.g., benzodiazepines, azepanes) are currently in progress in our laboratory and will be reported in due course.

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10. (2-{{[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-phenylcarbamoyl]-phenyl-methyl}-[2,2-difluoro-3-(2-hydroxy-1 *R*-phenylethylamino)-3 *S*-phenylpropionyl]-amino}-phenyl)-carbamic acid *tert*-butyl ester **5m**: All compounds were diluted in dry MeOH to afford a concentration of approximately 1 M. *N*-Boc-phenylenediamine (112 mg, 0.54 mmol, 1.2 equiv) and benzaldehyde (0.069 mL, 0.675 mmol, 1.5 equiv) were combined and the reaction was stirred for 2 h. Isonitrile (167 mg, 0.675 mmol, 1.5 equiv) and 2,2-difluoro-3-(2-hydroxy-1 *R*-phenylethylamino)-3 *S*-phenylpropionic acid (286 mg, 0.45 mmol, 1 equiv) were added, and the reaction was stirred for 24 h. After the solvent had been evaporated, the residue was purified on silica gel, eluting with cyclohexane/ethyl acetate gradient (9/1 to 7/3). ^{1}H NMR ($CDCl_3$) (300 MHz). Mixture of rotamers (ratio, 3/1); for clarity only one rotamer is described; 1st diastereoisomer: 0.0 (s, 6H), 0.8 (s, 9H), 1.6 (s, 9H), 3.7–4.0 (m, 2H), 4.6–5.0 (m, 4H), 6.2 (s, 1H), 6.7 (s, 1H), 6.72 (s, 1H), 7.0–7.6 (m, 21H), 8.05 (m, 1H), 8.5 (m, 1H), 9.1 (s, 1H), 10.0 (s, 1H); 2nd diastereoisomer: 0.0 (s, 6H), 0.8 (s, 9H), 1.6 (s, 9H), 3.7–4.0 (m, 2H), 4.6–5.0 (m, 4H), 6.2 (s, 1H), 6.7 (s, 1H), 6.72 (s, 1H), 7.0–7.6 (m, 21H), 8.1 (m, 1H), 8.4 (m, 1H), 9.2 (s, 1H), 10.1 (s, 1H). ^{19}F NMR ($CDCl_3$) (282 MHz). 1st diastereoisomer: −98.3 (d, 1F, $^2J_{F-F} = 271.9$ Hz), −98.8 (d, minor rotamer,

$^{2}J_{F-F} = 270.8$ Hz), −119.4 (dd, minor rotamer, $^{2}J_{F-F} = 259$ Hz, $^{3}J_{F-H} = 19.3$ Hz), −119.5 (dd, $^{2}J_{F-F} = 270.8$ Hz, $^{3}J_{F-H} = 23.6$ Hz); 2nd diastereoisomer: −98.9 (d, 1F, $^{2}J_{F-F} = 278.3$ Hz), −112.3 (dd, 1F, $^{2}J_{F-F} = 278.3$ Hz, $^{3}J_{F-H} = 19.3$ Hz).

^{13}C NMR ($CDCl_3$) (75.4 MHz). Only one rotamer of the 2nd diastereoisomer is described: −5.4, −5.2, 18.2, 25.8, 25.9, 27.0, 28.4, 28.5, 30.3, 43.6, 62.6, 65.4, 66.4, 68.7, 80.2, 117.5 (dd, $^{1}J_{C-F} = 208.9$ Hz, $^{1}J_{C-F} = 198.6$ Hz), 119.1, 121.0, 122.2, 124.4, 127.4, 127.5, 127.6, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.1, 129.4, 129.6, 130.6, 130.7, 131.0, 135.1, 137.5, 141.7, 153.5, 168.7.

R_f. 1st diastereoisomer: 0.58 (ethyl/cyclohexane 3/7); 2nd diastereoisomer: 0.47 (ethyl/cyclohexane 3/7).

Mass spectrometry (FAB+): $M = 865.3$.

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