ORGANIC LETTERS

2003
Vol. 5, No. 21
3887−3890

Stereocontrolled Synthesis of ψ[CH(CF_3)NH]Gly-Peptides

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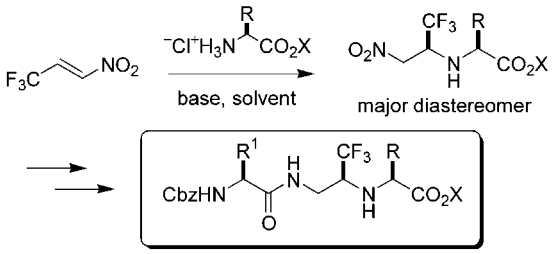
Received August 5, 2003

ABSTRACT



A novel class of peptidomimetics having a stereogenic [CH(CF_3)NH] replacement for a [CONH] peptide bond has been synthesized. The new compounds have been obtained in a stereocontrolled fashion using a kinetically controlled aza-Michael addition of chiral α-amino acid esters to *trans*-3,3,3-trifluoro-1-nitropropene. The stereoselectivity is strongly influenced by the solvent, the base, its stoichiometry, and the R side-chain. Diastereomeric ratios higher than 11:1 were achieved using H-Val-O*t*Bu·HCl in toluene with 1.1 equiv of DIPEA.

Backbone modification with replacement of one or more peptide bonds[1] is a well-established strategy for (1) circumventing some of the pharmacological drawbacks of peptides such as low in vivo bio-availability and adverse ADMET parameters[2] and (2) generating unnatural oligomers with a strong tendency to adopt specific and predictable conformations in solution ("foldamers").[3]

Recently, within the frame of a broad project aimed at the investigation of the "fluorine-effect" in peptides, we have described the synthesis and some structural and conformational features of a new class of fluorinated retropeptides **A** (Figure 1) having a [CH(CF_3)NH] unit instead of the natural

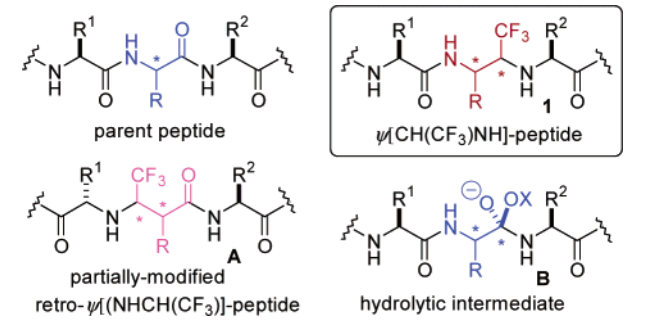


Figure 1. Structure of natural and ψ[CH(CF_3)NH]Gly-peptides.

[CONH] peptide bond.[4] This unit is a sort of hybrid between a peptide bond mimic and a proteolytic transition state analogue, as it combines some of the properties of a peptidyl −CONH− group (low NH basicity, a CH(CF_3)−NH−CH backbone angle close to 120°, a C−CF_3 bond substantially isopolar with the C=O) with properties of the tetrahedral intermediate **B** (Figure 1) involved in the protease-mediated

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(3) (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (c) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131−3152.

10.1021/ol0354730 CCC: $25.00
Published on Web 09/18/2003

Table 1. Results of the Aza-Michael Reaction.

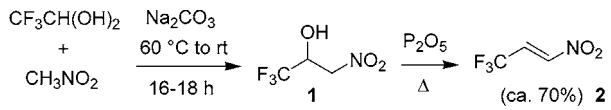
entry	α-amino ester	major product	R	X	base, solvent, *T* (°C)	dr[b]	yield (%)
1	L-**3a**	**4a**	*i*Pr	Bn	$NaHCO_3$ (1.1 equiv), DCM, rt	1.7:1.0	>98[b]
2	L-**3a**	**4a**	*i*Pr	Bn	TMP (1.1 equiv), DCM, rt	2.5:1.0	>98[b]
3	L-**3a**	**4a**	*i*Pr	Bn	DABCO (1.1 equiv), DCM, rt	3.0:1.0	79[c]
4	L-**3a**	**4a**	*i*Pr	Bn	DIPEA (1.1 equiv), DCM, rt	4.4:1.0	70[c]
5	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (1.1 equiv), THF, rt	3.7:1.0	>98[b]
6	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (1.1 equiv), CCl_4, rt	7.9:1.0	>98[b]
7	L-**3a**	**4a**	*i*Pr	Bn	DIPEA (1.1 equiv), toluene, rt	11.2:1.0	79[c]
8	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (1.1 equiv), toluene, rt	11.7:1.0	65[b]
9	L-**3b**	**4b**	*i*Pr	*t*Bu	none,[a] toluene, rt	3.8:1.0	>98[b]
10	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (1.0 equiv), toluene, rt	4.0:1.0	93[b]
11	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (1.3 equiv), toluene, rt	8.5:1.0	88[b]
12	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (1.5 equiv), toluene, rt	5.1:1.0	77[b]
13	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (1.7 equiv), toluene, rt	3.6:1.0	70[b]
14	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (2.0 equiv), toluene, rt	3.7:1.0	75[b]
15	L-**3b**	**4b**	*i*Pr	*t*Bu	DIPEA (5.0 equiv), toluene, rt	3.2:1.0	74[b]
16	L-**3c**	**4c**	Me	*t*Bu	DIPEA (1.1 equiv), toluene, rt	5.8:1.0	60[c]
17	L-**3c**	**4c**	Me	*t*Bu	none,[a] toluene, rt	1.6:1.0	87[c]
18	L-**3d**	**4d**	*s*Bu	Me	DIPEA (1.1 equiv), toluene, rt	7.5:1.0	72[c]
19	L-**3d**	**4d**	*s*Bu	Me	none,[a] toluene, rt	4.4:1.0	88[c]
20	L-**3e**	**4e**	Bn	*t*Bu	DIPEA (1.1 equiv), toluene, rt	8.5:1.0	60[c]
21	D-**3f**	*ent*-**4f**	Bn	Me	none,[a] toluene, rt	1.8:1.0	98[c]

[a] α-Amino ester was preliminarily treated with $NaHCO_3$. [b] Determined by ^{19}F and ^1H NMR. [c] Overall isolated yields.

hydrolysis reaction of a peptide bond (high electron density on the trifluoromethyl group, tetrahedral backbone carbon). Moreover, the presence of the bulky CF_3 group is probably the driving force for the high stability of turn-like conformations of appropriately configured retropeptides **A** both in low polarity organic solvent solutions and in the solid state. In this paper, we report a significant advancement of our project, consisting of the stereocontrolled synthesis of brand new peptidomimetics, much closer to natural peptides, having a fluoroalkyl backbone modification: ψ[CH(CF_3)NH]Gly-peptides **1** (Figure 1, R = H).

trans-3,3,3-Trifluoro-1-nitropropene **2** (Scheme 1) was prepared by a Henry reaction[5] of hydrate fluoral with an

Scheme 1. Synthesis of the Nitro-alkene



excess of nitromethane, followed by dehydration on P_2O_5 of the intermediate nitroaldol **1** and distillation.[6]

The key aza-Michael reactions between **2** (1.5 equiv) and an array of α-amino esters,[7] generated in situ from the hydrochlorides **3** (1.0 equiv) with a base, were operatively very simple and took place almost instantaneously at room temperature, affording the diastereomeric α′-Tfm-β′-nitro α-amino esters **4** (major) and **5** (minor).[8]

The diastereomers **4** and **5** were obtained in chemically and stereoisomerically pure form by flash chromatography.

The diastereoselectivity of the process was studied in detail conducting model reactions with L-Val benzyl and *tert*-butyl ester hydrochlorides **3a**,**b**. We found that the diastereoselectivity depends mainly on four reaction parameters: (1) the base, (2) the solvent, (3) the stoichiometry of the base, (4) and the R side chain of **3**. We first investigated the effect of the base (1.1 equiv in dichloromethane, DCM) on the diastereoselectivity (Table 1, entries 1−4). Modest stereocontrol was achieved with $NaHCO_3$, and slightly better with TMP (*sym*-collidine) and DABCO (1,4-diazabicyclo[2.2.2]-octane) (entries 1−3, respectively). The best result was observed with DIPEA (diisopropylethylamine) (63% de, entry 4).

(4) (a) Volonterio, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827−1830. (b) Volonterio, A.; Bravo, P.; Zanda, M. *Tetrahedron Lett.* **2001**, *42*, 3141−3144. (c) Volonterio, A. Bellosta, S.; Bravo, P.; Canavesi, M.; Corradi, E.; Meille, S. V.; Monetti, M.; Moussier, N.; Zanda, M. *Eur. J. Org. Chem.* **2002**, 428−438. (d) Volonterio, A.; Bellosta, S.; Bravin, F.; Bellucci, M. C.; Bruché, L.; Colombo, G.; Malpezzi, L.; Mazzini, S.; Meille, S. V.; Meli, M.; Ramírez de Arellano, C.; Zanda, M. *Chem. Eur. J.* **2003**, in press. "Fluorine-effect" refers to the unique modification of chemical, physical, biophysiological, and pharmacological properties of fluorinated molecules brought about by fluorine atom(s).

(5) For a review, see: Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915−945.

(6) Klenz, O.; Evers, R.; Miethchen, R.; Michalik, M. *J. Fluorine Chem.* **1997**, *81*, 205−210 and references therein.

(7) For a review of asymmetric conjugate additions to nitroalkenes, see: Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689−11698 and references therein.

(8) **Typical Procedure.** To a stirred solution of **2** (0.84 mmol, 119 mg) and **3a** (0.88 mmol, 216 mg) in toluene (3 mL) was added DIPEA (0.93 mmol, 160 μL) at room temperature. After 0.5 h at room temperature, the solvent was removed in vacuo, and the crude was dissolved in EtOAc and washed once with 1 N HCl. The organic layer was dried over anhydrous Na_2SO_4. The crude was purified by FC (hexane/diisopropyl ether 9:1) affording 232 mg (79%) of the two diastereoisomers **4a** and **5a** in an 11.0:1 ratio.

The effect of the solvent was investigated next (entries 4−8) using DIPEA (1.1 equiv) as a base. As recently observed for a tandem process involving an aza-Michael reaction with fluorinated acceptors,[9] we found that low-polarity or apolar solvents provided remarkably higher diastereocontrol. Thus, DCM (entry 4) and THF (entry 5) afforded modest des, while less polar toluene increased the de to 84% (entries 7 and 8). Intermediate results were observed using apolar CCl_4 (entry 6).

Surprisingly, the stoichiometry of DIPEA was also found to have a profound effect on the stereocontrol. In the absence of *free* DIPEA (entries 9 and 10),[10] the de dropped dramatically. Accordingly, a progressive decrease of stereoselectivity was observed by increasing the amount of DIPEA from 1.1 to 1.7 (entries 11−13), whereas little variation occurred beyond this quantity (entries 14 and 15). Further experiments (not included in Table 1) showed that other bases such as TMP and $NaHCO_3$ do not feature the same "stoichiometry-effect", affording comparable des upon changing the number of equivalents used.

No interconversion took place when pure diastereomers **4** and **5** were submitted to the exact reaction conditions for up to 16 h. Furthermore, no effect of the reaction time on the stereocontrol was detected. These aza-Michael reactions must therefore occur under kinetic control.

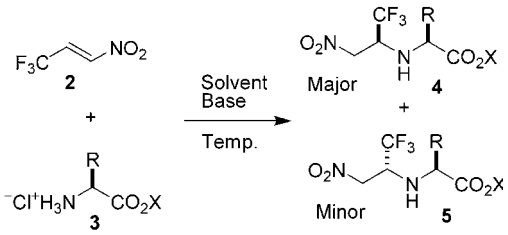
The effect of the R side chain of **3** is evident taking into account the reaction of different α-amino esters under the optimized conditions. In fact, less bulky R groups gave rise to lower degrees of stereocontrol in comparison with **4a**,**b**, as observed for L-Ala-O*t*Bu **3c** (71% de, entry 16) and L-Phe-O*t*Bu **3e** (79% de, entry 20).

An important effect of the stereogenic *sec*-butyl side-chain is more than likely in the case of L-Ile-OMe **3d** (77% de, entry 18), so this result should be weighted in a different manner.

Ancillary experiments showed that the ester group X of **3** has a negligible effect (compare entries 7 and 8). In contrast, the temperature is very important. Room temperature is essential in order to achieve high yields, whereas at both −40 and −70 °C, very complex mixtures of products were obtained. This rather surprising finding can be interpreted by supposing that at low temperatures there are several competitive side-processes, whereas the formation of **4** and **5** is favored at higher temperatures.

All the experimental evidence above suggests that this aza-Michael reaction involves a tight, polar, termolecular transition state (TS), involving **2**, **3**, and DIPEA, which appears to play a fundamental catalytic role.[11] Polar solvents, as well as the presence of more than one molecule of DIPEA in the TS, may disrupt it, thus lowering the stereocontrol.

Scheme 2. Aza-Michael Reaction

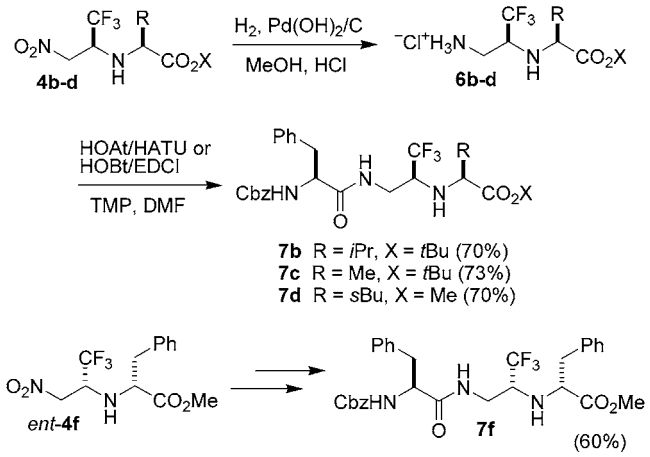


The main drawback of the use of DIPEA as the base is that somewhat modest yields were achieved in most cases (60−72%). Optimal yields (87−98%) were obtained using free α-amino esters (entries 11, 13, 15, 17), generated upon preliminary treatment of **3** with aqueous $NaHCO_3$, but in this case, the diastereoselectivities were remarkably lower.

The stereochemistry of the minor diastereomer **5a** was assessed by X-ray diffraction, whereas the configurations of the other adducts **4** and **5** were confidentially assigned on the basis of their spectroscopic and analytical features in comparison with those of **4a** and **5a**.[12]

Elaboration of the major adducts **4** into the target ψ[CH(CF_3)NH]Gly-peptides **7** (Scheme 3) was addressed

Scheme 3. Elaboration of the Aza-Michael Adducts **4** into ψ[CH(CF_3)NH]Gly-Peptides **7**



next. The nitro group of **4b**−**d** was hydrogenated to an amino group using Pearlman's catalyst (Scheme 3); the diamino compounds **6b**−**d** were trapped as hydrochlorides and submitted without purification to coupling with Cbz-L-Phe-OH, affording the ψ[CH(CF_3)NH]Gly tripeptides **7b**−**d** in good overall yields. Analogously, the nitro-adduct *ent*-**4f** derived from D-Phe-OMe was transformed into Cbz-L-Phe-ψ-[CH(CF_3)NH]Gly-D-Phe-OMe **7f**.

(9) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063. However, it should be stressed that the two processes are conceptually and mechanistically unrelated, since the stereocontrol of the reaction described in the reference above arose from an enolate protonation following the aza-Michael reaction, that per se was not stereogenic.

(10) In the experiment of entry 9, DIPEA was not added at all, whereas in entry 10 (1.0 equiv added), it is completely neutralized as hydrochloric acid salt.

(11) Catalytic effect of amine bases in Michael-type reactions is well-known. See for example: (a) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed.* **2002**, *41*, 338−340 and references therein. (b) van Axel Castelli, V.; Dalla Cort, A.; Mandolini, L.; Reinhoudt, D. N.; Schiaffino, L. *Eur. J. Org. Chem.* **2003**, 627−633.

(12) Full X-ray data and criteria for the stereochemistry assignments will be published in a full paper.

An in depth study of the aza-Michael reaction mechanism and an investigation of the conformational, structural, and biological properties of ψ[CH(CF_3)NH]Gly-peptides are currently underway. A synthesis of more complex ψ[CH(CF_3)NH]-peptides incorporating Tfm-analogues of chiral amino acids, rather than Gly, is being developed.

Acknowledgment. We thank the European Commission (IHP Network Grant "FLUOR MMPI" HPRN-CT-2002-00181), MIUR (Cofin 2002, Project "Peptidi Sintetici Bioattivi"), Politecnico di Milano, and C.N.R. for financial support.

Supporting Information Available: Detailed descriptions of experimental procedures and spectral data of compounds **4**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0354730