

Synthesis of mono N^α -trifluoroethylated cyclic dipeptides

Darryl D. DesMarteau* and Changqing Lu

Department of Chemistry, Clemson University, Clemson, SC 29634-0973, USA

Received 9 June 2005; revised 3 November 2005; accepted 8 November 2005

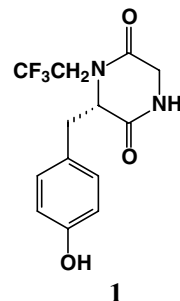
Available online 28 November 2005

Abstract—Trifluoroethylated N-termini in linear dipeptides L-TyrXOR [X = Gly, D-Ala, L-Leu, L-Phe, and L-Glu; R = H, Me, Et] exhibit sufficient nucleophilicity to give piperazine-2,5-dione ring formation through intramolecular cyclization reaction in acidic aqueous solutions. The reactions occur in high yield and with absolute configuration retention.
© 2005 Elsevier Ltd. All rights reserved.

Cyclic peptides are one class of naturally occurring privileged structures.¹ In comparison to linear peptides, cyclic peptides are more bioavailable and more stable to degradative peptidases.^{1,2} Cyclic dipeptides (piperazine-2,5-diones or 2,5-diketopiperazines DKPs) are among the simplest peptide derivatives commonly found in nature.^{3,4} They are a small, conformationally constrained heterocyclic scaffold that orientates its substituents in a spatially defined manner,^{5,6} and they are typically stable to proteolysis.^{7,8} These characteristics make cyclic dipeptides attractive scaffolds for medicinal chemistry,^{9–13} as well as agricultural applications.¹⁴ The earliest report of what was later found to be a cyclic dipeptide, *cyclo*-[Leu-Leu], dates back to 1849.¹⁵ The spontaneous formation of *cyclo*-[Gly-Gly] from moist H-Gly-OEt was reported in 1883.¹⁶ Soon, it was realized that cyclic dipeptides could be synthesized efficiently from amino acid esters.¹⁷ Since then, numerous symmetrical and unsymmetrical cyclic dipeptides have been prepared through both solution phase and solid phase synthesis, followed by cyclization reactions.^{13,18–22} The cyclization reactions have been shown to be either acid or base catalyzed.^{18,20,22–24}

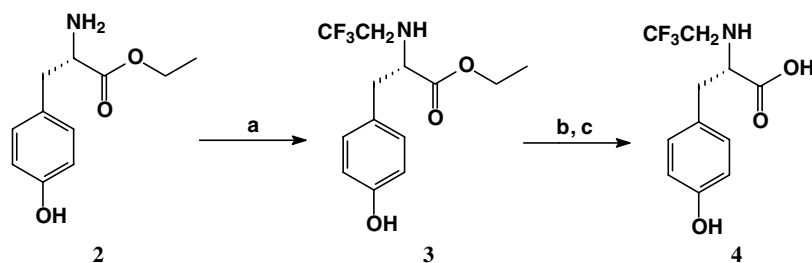
We have successfully transferred the trifluoroethyl group (CF_3CH_2-) to the functionalities, $-\text{SH}$, $-\text{NH}_2$, $-\text{NH}-$, $-\text{COOH}$, and $-\text{OH}$, of α -amino acids using the novel iodonium salt $\text{CF}_3\text{CH}_2\text{I}(\text{C}_6\text{H}_5)\text{N}(\text{SO}_2\text{CF}_3)_2$.^{25,26}

Once the CF_3CH_2- group is transferred to the N^α -group of amino acids, it acts as a protecting group (like Boc, Fmoc, Z, etc.) in conventional peptide synthesis except that it is not removable under standard deprotection conditions. Therefore, N^α -trifluoroethylated amino acids have been used as the N-terminus in peptide synthesis.²⁷ The question of whether or not the CF_3CH_2- group is an absolute protecting group for α -amino acids under any circumstances has not been answered. Previously we showed that $\text{p}K_2$ for N^α - CF_3CH_2 -GlyOH·HCl was 5.3, compared to $\text{p}K_a$ 5.6 for $\text{CF}_3\text{CH}_2\text{NH}_2\cdot\text{HCl}$. While the latter will couple with Z-PheOH, the former did not under the same conditions. Since $\text{CF}_3\text{CH}_2\text{-NHCH}(\text{CH}_3)\text{Ph}$ and $\text{CF}_3\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ph}$ also failed to undergo coupling under the same conditions, it was reasoned that steric factors were probably important, in addition to the decreased basicity of the nitrogen.²⁶ Herein, we report the unexpected formation of 3-(*S*)-[[4-(4-hydroxyphenyl)methyl]-4-[(2,2,2-trifluoro)ethyl]-2,5-piperazinedione **1** and its analogues via intramolecular cyclization at the nitrogen of N^α -trifluoroethylated amino acids.



Keywords: Trifluoroethylation; Nucleophilicity; Intramolecular cyclization; Cyclic dipeptide.

* Corresponding author. Tel.: +1 864 656 4705; fax: +1 864 656 0627; e-mail: fluorin@clemson.edu



Scheme 1. Reagents and conditions: (a) $\text{CF}_3\text{CH}_2\text{I}$, $(\text{C}_6\text{H}_5)\text{N}(\text{SO}_2\text{CF}_3)_2$, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, NaHCO_3 , rt, 3 h; (b) 1 M NaOH, rt, 10 h; (c) 0°C , concd HCl to pH 4.5, overall 95% for **4**.

The linear dipeptide ester $N^\alpha\text{-CF}_3\text{CH}_2\text{-L-Tyr-Gly-OEt}$ **5** was synthesized as follows. The reaction of L-tyrosine ethyl ester **2** with trifluoroethyl phenyliodonium bis((trifluoromethyl)sulfonyl)imide $\text{CF}_3\text{CH}_2\text{I}(\text{C}_6\text{H}_5)\text{N}(\text{SO}_2\text{CF}_3)_2$ in the two phase solvents $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ resulted in N^α -trifluoroethylated L-tyrosine ethyl ester **3**. The ethyl ester was then cleaved by basic hydrolysis followed by acidification with conc. HCl to pH between 4 and 5 to give N^α -trifluoroethylated L-tyrosine **4** (Scheme 1). The dipeptide ester **5** was synthesized in solution phase by coupling **4** with glycine ethyl ester (Scheme 2).

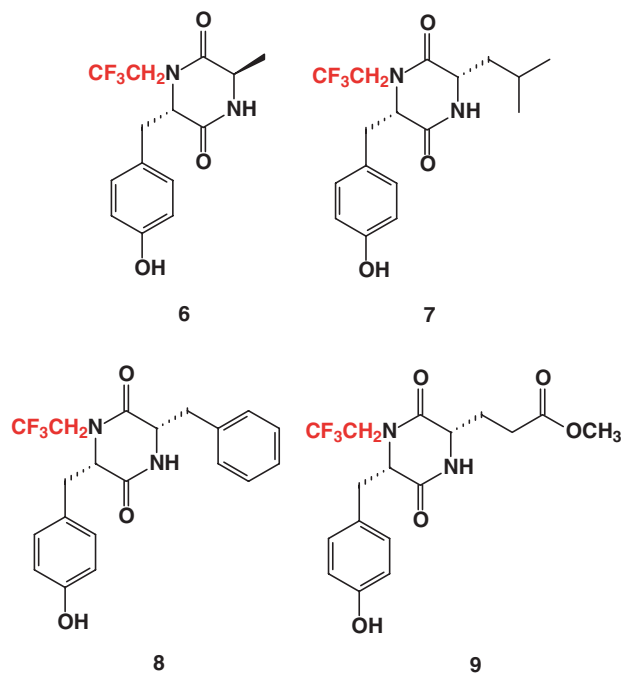
Cyclic dipeptides have been shown to spontaneously form from amino acid esters under mild conditions,^{3,16,28} although amino ester salts are usually stable as solids. The identity of the amino acid may determine the degree to which spontaneous cyclic dipeptide formation occurs.²² Cyclic dipeptide formation, today regarded by peptide chemists mostly as a troublesome side reaction during peptide chain assembly,^{29–32} actually represented the first successful attempt at linking two α -amino acids through a peptide bond.^{33,34} Most symmetrical cyclic dipeptides can be synthesized simply by heating the free amino acid esters.¹⁸ The unsymmetrical cyclic dipeptides could be synthesized by treating dipeptide esters with methanolic ammonia. However, the strongly basic conditions in this procedure could result in epimerization.³⁵ The other methods less prone to loss of chiral integrity had also been developed. Lichtenstein³⁶ used molten β -naphthol at $135\text{--}140^\circ\text{C}$ as the solvent for the cyclization of peptides. Kopple and Ghazarian³⁷ developed a one-step conversion of unblocked dipeptides or their hydrobromide salts to cyclic dipeptides in hot phenol. Dipeptide esters were cyclized in boiling 2-butanol/toluene mixtures³⁸ or in refluxing 2-butanol containing 0.1 M HOAc.³⁹ For many cyclic dipeptides, however, simple reflux of dipeptidyl methyl esters in low-boiling solvents, particularly methanol, was effective.⁴⁰ Thermal polymerization at $170\text{--}180^\circ\text{C}$ also provided cyclic dipeptides.^{41,42}

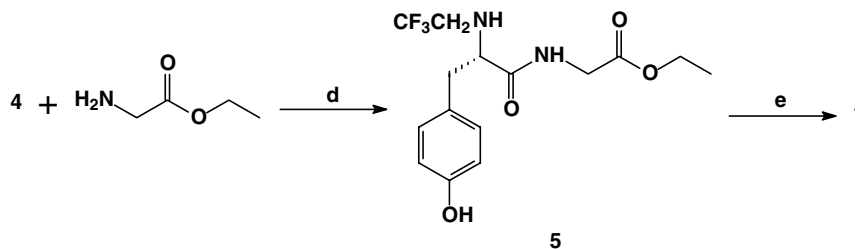
Initially, we did not expect the trifluoroethylated α -amino group in the linear dipeptides to have much reactivity as a nucleophile.²⁶ A sample of the linear dipeptide **5** was left in acidic aqueous solution at room temperature for 2 months and crystals were observed. These unexpected crystals were subjected to X-ray structure analysis, which showed that the linear dipeptide of **5** had cyclized to piperazine-2,5-dione. Subsequently, the cycli-

zation of **5** was carried out in refluxing acidic aqueous solution for 14 h to give **1** in 83% yield.

The X-ray structure of **1** is shown in Figure 1. The piperazine-2,5-dione ring is not planar, but slightly buckles toward the boat conformation. Compound **1** has a folded conformation in which the piperazine-2,5-dione ring faces the aromatic ring. This conformation is believed to result from either the interaction between amide dipoles and dipoles induced in the aromatic π electron cloud⁴³ or a $\text{C}(4)\text{H}/\pi$ interaction.⁴⁴ The π - π donor-acceptor interaction is not a major factor in stabilizing the face-to-face arrangement of rings.⁴⁵ The crystal of *cyclo*-[N^α -trifluoroethyl-L-tyrosyl-glycine] **1** is monoclinic (space group $P2_1$), which is different from orthorhombic (space group $P2_12_12_1$)^{46,47} reported for *cyclo*-[glycyl-L-tyrosine], presumably because of introduction of CF_3CH_2 - group onto the nitrogen atom of L-tyrosine in **1**.

Similarly, several other trifluoroethylated cyclic dipeptides **6–9** were synthesized in high yields (82–95% via cyclization reaction). Both NMR data and X-ray structure analysis confirmed the absolute configuration retention of all chiral centers.





Scheme 2. Reagents and conditions: (d) HOBt, EDAC, DIPEA, CH_2Cl_2 , 0 °C to rt, 6 h, 93%; (e) H_2O , concd HCl to pH 0.5, reflux, 14 h, 83% for **1**.

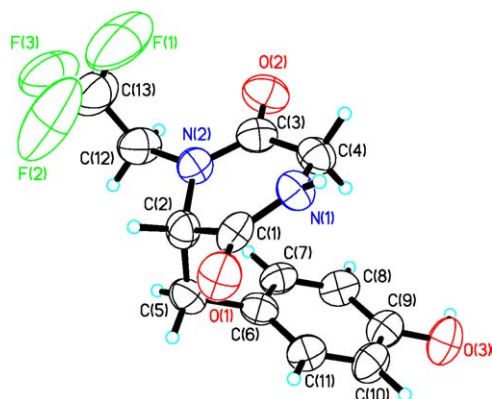


Figure 1. Crystal structure of **1**.

Under the same conditions, the Fmoc-protected linear dipeptide Fmoc-Gly-Phe-OMe did not undergo the cyclization reaction.

From these results it is clear that the trifluoroethylated N-termini in linear dipeptides can still undergo amide bond formation through intramolecular cyclization reaction in acidic aqueous solutions. Future work will be focused on the effects of bases on the cyclization reaction of N-terminal trifluoroethylated linear dipeptides, given the lowered pK_a of the trifluoroethylated N-termini.

Spectral data for **1**: δ_{H} (500.16 MHz, CD_3CN): 2.52 (1H, d, $J = 17.7$ Hz), 3.09 (2H, mc (centered multiplet)), 3.49 (1H, dd, $J = 17.7, 4.1$ Hz), 3.57 (1H, mc), 4.23 (0.5H, d, $J = 4.1$ Hz), 4.24 (0.5H, d, $J = 4.5$ Hz), 4.70 (1H, mc), 6.63 (1H, br s), 6.75 (2H, d, $J = 8.5$ Hz), 6.96 (2H, d, $J = 8.5$ Hz); δ_{F} (470.62 MHz, CD_3CN): -69.4 (3F, t, $J = 9.2$ Hz); δ_{C} (125.76 MHz, CD_3CN): 35.7, 43.6, 44.0 (q, $J = 33.6$ Hz), 62.6, 115.4, 124.7 (q, $J = 280.4$ Hz), 125.6, 131.3, 156.8, 166.1, 167.5; MS (EI) m/z : formula $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3\text{F}_3$, calcd 302.08, found 302.04.

Crystallographic data for **1**: Formula, $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3\text{F}_3$; monoclinic; $P2_1$; $T = 293(2)$ K; $a = 7.6822(15)$, $b = 10.906(2)$, $c = 8.7170(17)$ Å, $\beta = 106.16(3)^\circ$; $V = 701.5(2)$ Å³; $D_{\text{calc}} = 1.431$ g cm⁻³; $Z = 2$; $\mu = 0.128$ mm⁻¹; empirical absorption correction (0.9135–0.9272); Mo-K α radiation with graphite monochromator, $\lambda = 0.71073$ Å; Rigaku AFC-8S diffractometer; 7203 measured reflections ($R_{\text{int}} = 1.59\%$); 3068 reflec-

tions used with $I > 2\sigma(I)$; $2\theta_{\text{max}} = 54.94^\circ$; 238 parameters; non-H atoms refined anisotropically; H atoms fixed in calculated positions (C–H = 0.96 Å); full-matrix least-squares on F^2 refinement; $R = 3.88\%/R_w(F^2) = 10.14\%$. CCDC 233027.

Acknowledgments

Financial support of this research by the National Science Foundation is gratefully acknowledged. Crystallographic data were supplied by Dr. Don VanDerveer. We thank Dr. R. V. Rajagopal for useful discussions.

Supplementary data

The spectral data and crystallographic data of compounds **6–9** are included in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.038.

References and notes

- Horton, D. A.; Bourne, G. T.; Smythe, M. L. *J. Comput. Aided Mol. Des.* **2002**, *16*, 415–430.
- Kohli, R. M.; Walsh, C. T.; Burkart, M. D. *Nature* **2002**, *418*, 658–661.
- Prasad, C. *Peptides* **1995**, *16*, 151–164.
- Witiak, D. T.; Wei, Y. *Prog. Drug Res.* **1990**, *35*, 249–363.
- Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 627–650.
- Herbert, R. H.; Kelleher, F. *Tetrahedron Lett.* **1994**, *35*, 5497–5500.
- Morley, J. E.; Levine, A. S.; Prasad, C. *Brain Res.* **1981**, *210*, 475–478.
- Szardnangs, A. K.; Burkoth, T. S.; Lu, H. H.; Tien, D. W.; Campbell, D. A. *Tetrahedron* **1997**, *53*, 6573–6593.
- Rhee, K. H. *Int. J. Antimicrob. Agents* **2004**, *24*, 423–427.
- Cui, C.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651–12666.
- Funabashi, Y.; Horiguchi, T.; Iinuma, S.; Tanida, S.; Harada, S. *J. Antibiot.* **1994**, *47*, 1202–1218.
- Krchnak, V.; Weichsel, A. S.; Cabel, D.; Flegelova, Z.; Lebl, M. *Mol. Div.* **1996**, *1*, 149–164.
- Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 612–623.
- Ienaga, K.; Nakamura, K.; Kurohashi, M.; Nakanishi, T.; Ichii, T. *Phytochemistry* **1990**, *29*, 35–39.
- Bopp, F. *Liebigs Ann. Chem.* **1849**, *69*, 16–37.
- Curtius, T. *Chem. Ber.* **1883**, *16*, 753–757.

17. Curtius, T.; Goebel, F. *J. Prakt. Chem.* **1888**, 37, 173–181.
18. Fischer, P. M. *J. Peptide Sci.* **2003**, 9, 9–35.
19. Muller-Hartwig, J. C. D.; Akyel, K. G.; Zimmermann, J. *J. Peptide Sci.* **2003**, 9, 187–199.
20. Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, 58, 3297–3312.
21. Rodionov, I. L.; Rodionova, L. N.; Baidakova, L. K.; Romashko, A. M.; Balashova, T. A.; Ivanov, V. T. *Tetrahedron* **2002**, 58, 8515–8523.
22. del Fresno, M.; Alsina, J.; Royo, M.; Barany, G.; Albericio, F. *Tetrahedron Lett.* **1998**, 39, 2639–2642.
23. Akiyama, M.; Katoh, A.; Tsuchiya, Y. *J. Chem. Soc., Perkin Trans. 1* **1989**, 235–239.
24. Sollis, S. L. *J. Org. Chem.* **2005**, 70, 4735–4740.
25. DesMarteau, D. D.; Montanari, V. *Chem. Commun.* **1998**, 20, 2241–2242.
26. DesMarteau, D. D.; Montanari, V. *Chem. Lett.* **2000**, 9, 1052–1053.
27. DesMarteau, D. D.; Montanari, V. *J. Fluorine Chem.* **2001**, 109, 19–23.
28. Kertscher, U.; Bienert, M.; Krause, E.; Sepetov, N. F.; Mehli, B. *Int. J. Peptide Protein Res.* **1993**, 41, 207–211.
29. Goodman, M.; Stueben, K. C. *J. Am. Chem. Soc.* **1962**, 84, 1279–1283.
30. Gisin, B. F.; Merrifield, R. B. *J. Am. Chem. Soc.* **1972**, 94, 3102–3106.
31. Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, 107, 4936–4942.
32. Fischer, P. M.; Solbakken, M.; Undheim, K. *Tetrahedron* **1994**, 50, 2277–2288.
33. Kohler, A. *Liebigs Ann. Chem.* **1865**, 134, 367–372.
34. Fischer, E.; Forneau, E. *Chem. Ber.* **1901**, 34, 2868–2877.
35. Rosenmund, P.; Kaiser, K. *Angew. Chem., Int. Ed. Engl.* **1970**, 9, 162–163.
36. Lichtenstein, N. *J. Am. Chem. Soc.* **1938**, 60, 560–563.
37. Kopple, K. D.; Ghazarian, H. G. *J. Org. Chem.* **1968**, 33, 862–864.
38. Nitecki, D. E.; Halpern, B.; Westley, J. W. *J. Org. Chem.* **1968**, 33, 864–866.
39. Suzuki, K.; Sasaki, Y.; Endo, N.; Mihara, Y. *Chem. Pharm. Bull.* **1981**, 29, 233–237.
40. Ueda, T.; Saito, M.; Kato, T.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1983**, 56, 568–572.
41. Hartmann, J.; Brand, M. C.; Dose, K. *BioSystems* **1981**, 13, 141–147.
42. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1987**, 70, 102–115.
43. Kopple, K. D.; Marr, D. H. *J. Am. Chem. Soc.* **1967**, 89, 6193–6200.
44. Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Bioorg. Med. Chem.* **1999**, 7, 2021–2026.
45. Ziauddin; Kopple, K. D. *J. Org. Chem.* **1970**, 35, 253–255.
46. Webb, L. E.; Lin, C. *J. Am. Chem. Soc.* **1971**, 93, 3818–3819.
47. Lin, C.; Webb, L. E. *J. Am. Chem. Soc.* **1973**, 95, 6803–6811.