Tetrahedron Letters 50 (2009) 1048–1050

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Acyclic and cyclic thioenamino peptides: solution- and solid-phase synthesis

Lee Goren, Doron Pappo, Israel Goldberg, Yoel Kashman *

School of Chemistry, Tel-Aviv University, Ramat Aviv 69978, Israel

ARTICLE INFO

Article history:
Received 28 October 2008
Revised 8 December 2008
Accepted 16 December 2008
Available online 24 December 2008

Keywords:
Cyclic peptides
Solid-phase synthesis
FGly
Endiamine
Thioenamine

ABSTRACT

Seven- and 10-membered cyclic thioenamino peptides, that is, 1,4-thiazepinone (**11**) and cyclic thioenamino peptide **9** (which represents a potential γ-turn mimetic), were synthesized, and the structure of **11** was secured by X-ray diffraction analysis of its TFA salt. The aforementioned compounds were prepared in solution and by solid-phase synthesis. Additionally, we have prepared thioenamino diketopiperazine synthon **16**.

Callynormine A,[1] a new type of sponge-derived cyclic peptide, possessing an endiamino functionality, instead of the lactone of depsipeptides, has prompted the synthesis of cyclic endiamino and thioenamino peptides. Cyclic endiamino and thioenamino peptides are expected to be of interest because of their restricted conformations, and their potential ability to probe the topography of enzyme active sites and to generate inhibitors devoid of the typical therapeutic shortcomings of peptides. Moreover, thioenamino and endiamino peptides have been reported for their ability to mimic protein secondary structures.[2–4] Cyclization of 'alpha, omega' amino enol-tosylates is a good route for the preparation of cyclic thioenamino peptides.[2–7]

Herein, we describe reactions of formylglycine (FGly) in solution and with the hitherto unknown solid-supported FGly. It is shown that supported FGly reacts with amines and with nucleophilic thiols in the same manner as FGly-OTs in solution.

It is difficult to compare the yields obtained under solution- and solid-phase conditions, as no optimization of the latter reaction was attempted and the extent of the resin loading is unknown.

Preparation of linked solid phase FGly, for example, **2**, was carried out in two steps. First Swern oxidation of serine [$(COCl)_2$, DMSO, DIPEA, DCM, −78 °C] to the unstable α-formylglycine, followed by trapping of its enol tautomer with a sulfonyl chloride resin,[8] gave, after slow warming to room temperature, the desired polymer-supported FGly **2**.

Subsequently, we examined the reactivity of the supported FGly **2** toward reactions with nucleophiles. Overnight stirring of compound **2a** or **2b** with an amine or thiol in the presence of base led to endiamine **3**,[9] and thioenamino peptides **4**–**7** (Table 1). The structures of compounds **3**–**7** were elucidated from 1D and 2D ^{1}H NMR spectra and mass spectrometry.

The *Z* configuration of endiamine **3**,[2] and of thioenamino peptides **4**–**6** was deduced from the NOEs, observed, between the methoxy group and the vinyl proton. Compound **7**,[10] with the Cbz-protecting group, on the other hand, did not show a positive NOE correlation, and therefore is suggested to be of *E* configuration. (The NH signal could not be observed in $CDCl_3$ or in DMSO-d_6).

Among the secondary structures of peptides, reverse turns that include β- and γ-turns are known as structural elements that are involved in biomolecular recognition events.[11] In proteins or peptides, β-turns are characterized by a 10-membered ring incorporating a single hydrogen bond, and are more frequent than γ-turns which form seven-membered rings with a single hydrogen bond (Fig. 1).[12,13] The latter are found mainly in small peptides but are rare in proteins.

Compounds **9** (Scheme 2) and **11** (Scheme 1) were synthesized as model compounds. The cyclic seven-membered 1,4-thiazepinones **11** and **14** were synthesized from compound **10** in solution, or from **13** by solid-phase synthesis, respectively.

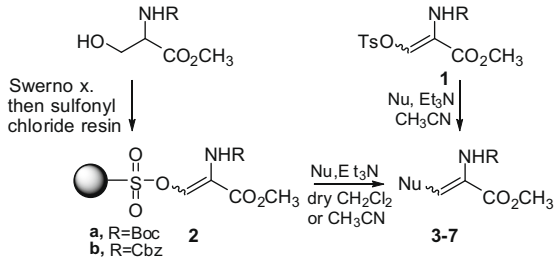
The preparation of 1,4-thiazepinone **11** was achieved from Boc-Cys(Tr)-Ser-OMe,[14] which was oxidized and trapped as the appropriate enol-tosylate **10** (Scheme 1). Deprotection with TFA (50%) of both the *N*-Boc and *S*-Tr-protecting groups, of **10**, followed by base-induced cyclization afforded compound **11**,[15] and with excess TFA, its salt **12**.

Compound **12** was obtained as crystals which enabled X-ray diffraction analysis to confirm the structure (Scheme 1).[16] Selective deprotection of the thiol group of **10** (Scheme 1) under mild acidic

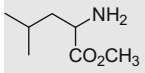
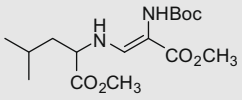
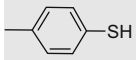
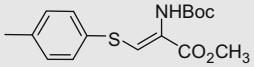
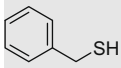
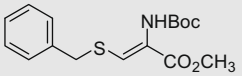
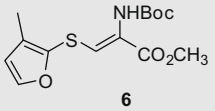
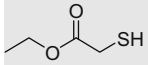
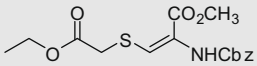
* Corresponding author. Fax: +972 3 6409293.
E-mail address: kashman@post.tau.ac.il (Y. Kashman).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.072

Table 1
Solid- and solution-phase synthesis of compounds **3–7**[a,b]



Nu=amine or thiol.

Nu	Product	Yield (%)
	 **3**	80
	 **4**	90
	 **5**	83
	 **6**	85
	 **7**	[c]

[a] Solution-phase synthesis: 1 equiv of nucleophile, 4–5 equiv of Et_3N. The yield shown is for the isolated product starting from the protected enol tosylate **1**.
[b] Solid-phase synthesis: 10 equiv of nucleophile, 15 equiv of Et_3N. The yield (not shown) of isolated product is calculated for the two steps (oxidation and nucleophilic substitution) based on 100% resin loading, and as the extent of the resin loading is unknown, it is difficult to compare the yields in solution and solid phase. For estimated yields, see Supplementary data.
[c] Performed only by solid-phase synthesis.

conditions (2% TFA), followed by addition of base, led to compound **14**.[17]

Next, the solid-supported FGly dipeptide **13**, obtained from Boc-Cys(Tr)-Ser-OMe, after selective deprotection of the thiol group, under mild acidic conditions (2% TFA), gave, as in solution, after treatment with base, the desired cyclic thioenamino peptide

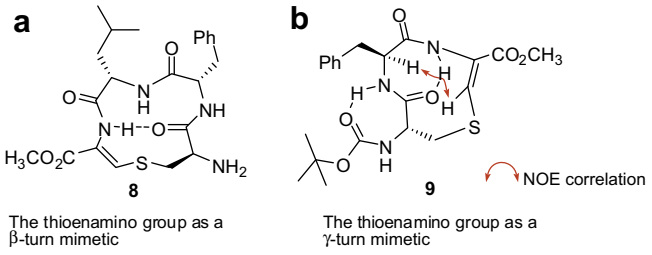
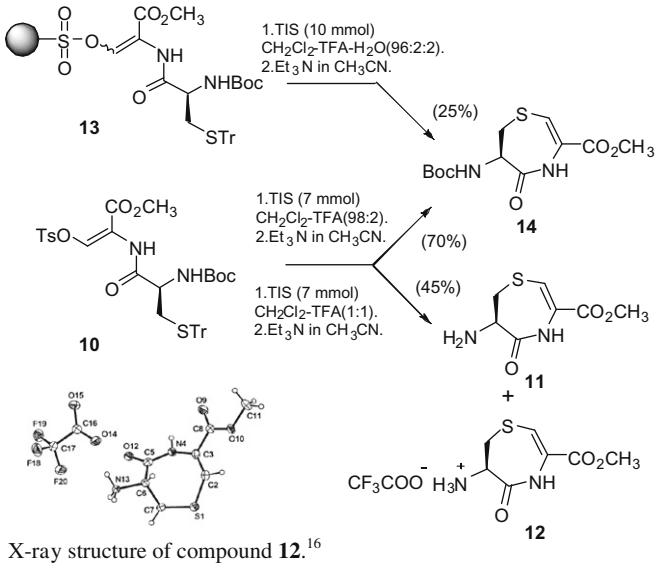


Figure 1. Cyclic thioenamines as turn-like mimetics: (a) β-turn tetrapeptide **8**,[3] involving a 10-membered hydrogen bond; (b) γ-turn compound **9**, containing a seven-membered hydrogen bond.



X-ray structure of compound **12**.[16]

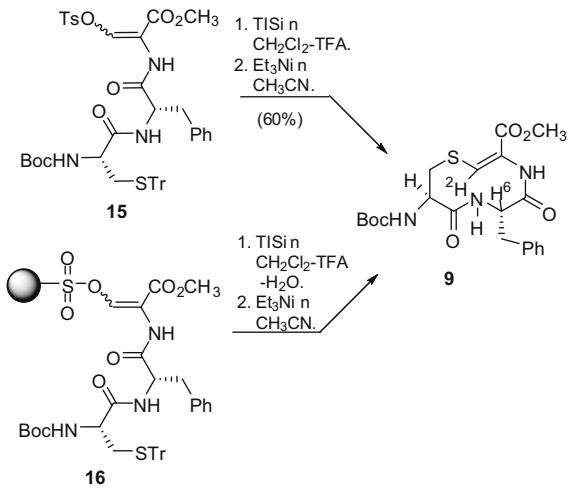
Scheme 1. The synthesis of 1,4-thiazepinones.

14 (Scheme 1). Another seven-membered cyclic thioenamino 1,4-thiazepinone,[18] prepared in a different way, has been reported for its therapeutic potential as an ACP/NEP dual inhibitor.[18]

The cyclic 10-membered thioenamino tripeptide **9** was synthesized both from compound **15** in solution, and from **16** by solid-phase synthesis (Scheme 2). The structure of **9** was confirmed by MS and 1D and 2D NMR including ^{15}NH-HMBC (Fig. 2).[19] A 2*E* configuration is suggested for **9** based on the NOE measured between H-2 and H-6, which is only possible, according to a model, for the 2*E* configuration. To the best of our knowledge, this is the first reported cyclic thioenamino peptide with an *E* configured double bond, formed most likely to relieve ring strain.

The β-turn of the previously synthesized cyclic thioenamino peptide **8**[3] is compared with the potential γ-turn of **9**, as suggested by NMR measurements (Fig. 1).

The configuration of **9** was confirmed by the temperature coefficients of the amide protons in DMSO-d_6.[20] Namely, a small coefficient was measured for the thioenamino NH proton (NH-FGly, −3.8 ppb/K), compared to the NH-Cys proton (−8.4 ppb/K). The NH-Phe proton exhibited an intermediate temperature coefficient (−4.5 ppb/K), most likely due to a hydrogen bond with the Boc carbonyl). The NH-FGly and NH-Phe coefficients indicated that they were both involved in intramolecular hydrogen bonds. The NOESY



Scheme 2. Synthesis of 10-membered cyclic thioenamino tripeptide **9**.

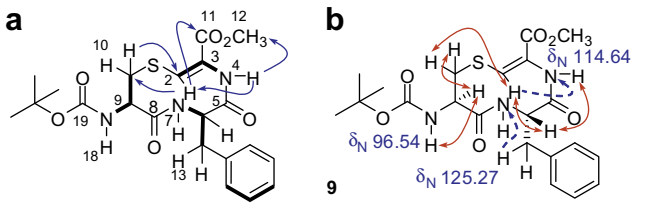
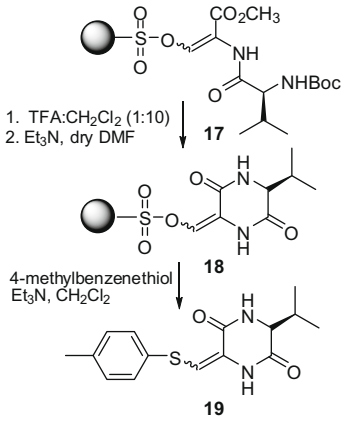


Figure 2. (a) (⌒) Selected ^{13}CH-HMBC and (▬) selected HH-COSY correlations and (b) (⌒) selected ^{15}NH-HMBC and selected (⌒) NOESY correlations for compound **9**.



Scheme 3. The solid-phase synthesis of a diketopiperazine synthon, and a thioenamino compound **19**.

transannular cross peak between the α-Phe proton (H-6) and the vinylic thioenamino proton (H-2, Fig. 2) further supported the possible γ-turn configuration.

Another application of the solid-phase methodology is demonstrated by the synthesis of diketopiperazine **19**,[18] which is a potentially interesting bioactive[21] synthon (Scheme 3).[22]

The solution synthesis of diketopiperazines via enol-tosylates was reported earlier by us.[3] The solid-phase synthesis requires two synthetic steps on the resin, that is, deprotection of the *N*-Boc group of compound **17** (synthesized from Val-Ser), with TFA, followed by base treatment to afford synthon **18**, which after thiol substitution afforded compound **19**.[23]

In summary, we have demonstrated two synthetic approaches, one in solution and a new solid-phase route, for the preparation of thioenamino and endiamino compounds. Inter alia, the synthesis of 1,4-thiazepinone **11** and of the 10-membered thioenamino cyclic tripeptide **9** was demonstrated. The latter compound most likely prefers a γ-turn-like conformation, hence being a potential γ-turn motif.

Reverse turn mimetics as prepared herewith are considered to be promising candidates for drug discovery due to their ability to function as agonists of important biological processes.[24]

Acknowledgments

We thank the Israeli Science Foundation for financial support, Grant # 180/05, Dr. Amira Rudi for her help with NMR measurements, Dr. Moshe Portnoy for helpful discussions, Ms. Yael Kogon for her contribution to this project, and Dr. Ayelet Sacher (of the Maiman Institute for Proteome Research, Tel Aviv University) for performing the electrospray mass measurements.

Supplementary data

Supplementary data (general procedures and spectral data (1D and 2D NMR) for selected compounds are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.072.

References and notes

1. Berer, N.; Rudi, A.; Goldberg, I.; Benayahu, Y.; Kashman, Y. *Org. Lett.* **2004**, *6*, 2543–2545.
2. Pappo, D.; Vartanian, M.; Lang, S.; Kashman, Y. *J. Am. Chem. Soc.* **2005**, *127*, 7682–7683.
3. Pappo, D.; Kashman, Y. *Org. Lett.* **2006**, *8*, 1177–1179.
4. Marshall, G. R. *Tetrahedron* **1993**, *49*, 3547–3558.
5. Chruszez, M.; Laidler, P.; Monkiewicz, M.; Ortlund, E.; Lebioda, L.; Lewinski, K. *J. Inorg. Biochem.* **2003**, *96*, 386–392.
6. It is suggested that cyclic endiamino peptides are obtained in Nature by the condensation of FGly (formylglycine) with the amine of an amino acid. FGly, which is known in Nature only as a hydrate in active sites of enzymes, is unstable in solution, and has therefore to be protected as, for example, enol-tosylate (FGly-OTs) **1**. The latter moiety was shown to function as the free aldehyde.
7. Nakazawa, T.; Suzuki, T.; Ishii, M. *Tetrahedron Lett.* **1997**, *38*, 8951–8954.
8. Sulfonyl chloride resin, Sigma–Aldrich, # 498211.
9. Compound **3**. Amorphous solid, HRESMS (*m/z* 345.2020 (M^+)).
10. The structure of compound **7**, obtained as an amorphous solid, was established from 1D and 2D NMR and HRESMS (*m/z* 376.0825 (M+Na^+)) data.
11. Smith, J. A.; Pease, L. G. *CRC Crit. Rev. Biochem.* **1980**, *8*, 315–399.
12. Examples of peptides forming γ-turns: (a) Levian-Teitlbaum, D.; Kolodny, N.; Chorev, M.; Selinger, Z.; Gilon, C. *Biopolymers* **1989**, *28*, 51–64; (b) Raghothama, S.; Ramakrishnan, C.; Balasubramanian, D.; Balaram, P. *Biopolymers* **1989**, *28*, 573–588; (c) Milon, A.; Miyazawa, T.; Higashijima, T. *Biochemistry* **1990**, *29*, 65–75; (d) Walse, B.; Kihlberg, J.; Drakenberg, T. *Eur. J. Biochem.* **1998**, *252*, 428–440.
13. For γ-turn mimetics, see: (a) Schmidt, B.; Lindman, S.; Tong, W.; Lindeberg, G.; Gogoll, A.; Lai, Z.; Thörnwall, M.; Synnergren, B.; Nilsson, A.; Welch, C. J.; Sohtell, M.; Westerlund, C.; Nyberg, F.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 903–919; (b) Brickmann, K.; Yuan, Z.; Sethson, I.; Somfai, P.; Kihlberg, J. *Chem. Eur. J.* **1999**, *5*, 2241–2253; (c) Jiménez, A. I.; Cativiela, C.; Marraud, M. *Tetrahedron Lett.* **2000**, *41*, 5353–5356.
14. Boc-Cys(Tr)-Phe-Ser-OMe was prepared by standard peptide synthesis procedures. Its structure was established by 1D and 2D NMR and HRESMS (*m/z* 734.2878 (M+Na^+)) data.
15. The structure of compound **11**, a yellow oil, was established from 1D and 2D NMR and HRESMS (*m/z* 203.0484 (M^+)) data. Inter alia, the HMBC experiment showed a correlation between H-2 and C-7 in the ring. A characteristic vinylic thioenamino proton resonance at δ 7.12 (s) ppm, and the corresponding carbon at δ 121.1 ppm were present.
16. The structure of compound **12** was confirmed by single crystal X-ray diffraction analysis (Scheme 1). The measurements were carried out on a Nonius KappaCCD diffractometer at low temperature (ca. 110 K) in order to optimize the precision of the crystallographic determination, with Mo Kα radiation. *Crystal data:* $C_7H_{11}N_2O_3S$, M = 316.26, triclinic, space group $P1$, a = 4.9238(6), b = 5.9807(7), c = 11.4838(8) Å, α = 73.489(7)°, β = 89.571(7)°, γ = 75.771(5)°, V = 313.57(6) Å^3, Z = 1, T = 110(2) K, D_c = 1.675 g cm^{-3}, μ(Mo Kα) = 0.32 mm^{-1} 2014 unique reflections to $2\theta_{max}$ = 53.0°, 184 refined parameters, R_1 = 0.046 for 1772 observations with $I > 2\sigma(I)$, R_1 = 0.056 (wR_2 = 0.103) for all unique data. Crystal data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC 709744. The supplementary crystallographic data for this Letter can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1233 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/).
17. The structure of compound **14**, an amorphous solid, was established from ^{1}H, ^{13}C NMR, and HRESMS (*m/z* 325.0828 (M+Na^+)) data. The characteristic vinylic thioenamino proton resonance at δ 7.20 (s) ppm, and the corresponding carbon at δ 120.9 ppm were present.
18. [*S*-(*R**,*S**)]-6-[(2-Mercapto-1-oxo-3-phenylpropyl)amino]-4,5,6,7-tetrahydro-2-methyl-5-oxo-1,4-thiazepine-3-carboxylic acid has been reported for its therapeutic potential as an ACP/NEP dual inhibitor. Crescenza, A.; Botta, M.; Corelli, F.; Santini, A.; Tafi, A. *J. Org. Chem.* **1999**, *64*, 3019–3025.
19. Compound **9**, amorphous solid, HRESMS (*m/z* 472.1515 (M+Na^+)). The characteristic vinylic thioenamino proton resonance at δ 7.39 (s) ppm, and carbon resonance at δ 144.5 ppm were present.
20. (a) Well, R. M. V.; Marinelli, L.; Altona, C.; Erkelens, K.; Siegal, G.; Raaij, M. V.; Liamas- Saiz, A. L.; Kessler, H.; Novellino, E.; Lavecchia, A.; Van Boom, J. H.; Overhand, M. *J. Am. Chem. Soc.* **2003**, *125*, 10822–10829; (b) Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182–3188; (c) Jeannotte, G.; Lubell, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 14334–14335; (d) Xiao, J.; Weisblum, B.; Wipf, P. *J. Am. Chem. Soc.* **2005**, *127*, 5742–5743.
21. Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923–9932.
22. Fischer, P. M. *J. Peptide Sci.* **2003**, *9*, 9–35.
23. The structure of compound **19** (obtained as a white solid) was established from ^{1}H, ^{13}C NMR, and HRESMS (*m/z* 313.1009 (M+Na^+)) data. The characteristic vinylic thioenamino proton resonance at δ 6.64 (s) ppm, and carbon resonance at δ 122.9 ppm were present.
24. Disclosure of reverse-turn regions of biologically active peptides and proteins; Moon, S. H. U.S. Pat. Appl. Publ. 826, 972, 2007; *Chem. Abst.* 146, 274, 627.