Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5305-5308, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01100-8

The Solid Phase Synthesis of Oligoureas

Jong-Man Kim,[a] Yingzhi Bi,[b] Sari J. Paikoff,[a] Peter G. Schultz[a,*]

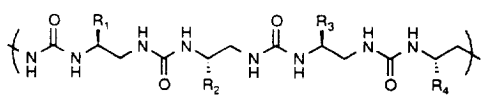
a. Howard Hughes Medical Institute
Department of Chemistry
University of California
Berkeley, CA 94720

b. Affymax Research Institute
4001 Miranda Avenue
Palo Alto, CA 94304

Abstract: An efficient method for solid phase synthesis of oligoureas from readily prepared optically active azido 4-nitrophenyl carbamate monomers is described. Copyright © 1996 Elsevier Science Ltd

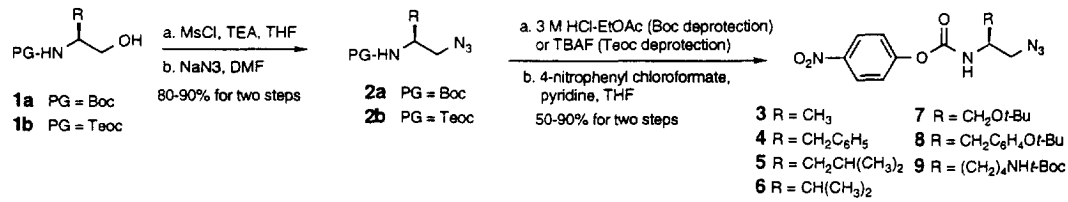
The peptide backbone provides a framework for constructing large folded polymers with a wide range of functions, as well as smaller oligomeric agonists, antagonists, and enzyme inhibitors. Advances in solid-phase synthetic methods have stimulated considerable interest both in protein design[1] and in the synthesis of structurally diverse peptide libraries that can be screened against biological targets.[2] Obstacles associated with the therapeutic use of peptides have led to efforts to develop new oligomeric backbones (carbamates, peptoids, ureas, sulfonamides, azatides) with improved pharmacological properties relative to peptides.[3] The ability to efficiently assemble large synthetic oligomers also provides an opportunity to generate unnatural polymers with defined secondary and tertiary structures. Such structures should provide increased insight into the relationships between monomer structure and polymer conformation and may provide new classes of folded polymers with novel properties.

As part of our efforts to explore a variety of backbone chemistries, we have investigated the synthesis of oligoureas with the general structure shown below. These oligomers have backbones with hydrogen bonding groups, chiral centers, a significant degree of conformational restriction, and sites (backbone NH) for the introduction of additional side chain groups that may further modulate the physical and biological properties of the oligomers.



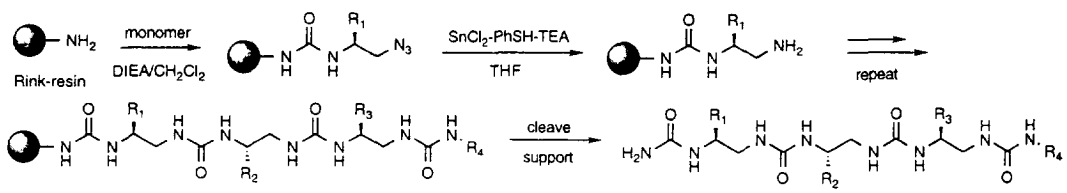
Burgess *et al.*[4] have recently reported a solid phase synthesis of a tetrameric urea using mono-phthalimide protected isocyanates as monomers. Removal of the phthalimide group with hydrazine, however, is slow and likely to limit side chain functionality. The synthesis reported here utilizes activated *p*-nitrophenyl carbamates and "protected" amines in the form of azides, which can be reduced with $SnCl_2$-thiophenol-triethylamine on solid support.[5]

Monomers with alkyl side-chains were prepared from *N*-Boc (*t*-butoxycarbonyl) protected amino alcohols **1a** while those with acid labile side-chains were synthesized from *N*-Teoc (2-(trimethylsilyl)ethoxycarbonyl) protected amino alcohols **1b** (Scheme 1). *N*-Boc protected amino alcohols were either commercially available or can be prepared by reduction of corresponding *N*-Boc protected amino acids.[6] *N*-Teoc protected amino alcohols were readily obtained by reacting side-chain protected amino alcohols[7] with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate. The *N*-Boc or *N*-Teoc protected amino alcohol **1a** or **1b** was converted to the corresponding *N*-Boc or *N*-Teoc protected azide **2a** or **2b** *via* mesylation (methanesulfonyl chloride, TEA, THF, 0 °C) followed by azide displacement (NaN_3, DMF, 55 to 60 °C) in high yield (80 -90%) for the two steps. The *N*-Boc and *N*-Teoc protecting groups were removed with aqueous HCl in EtOAc or TBAF in MeCN, respectively. The resulting free amine was converted to the activated monomers (**3-9**) by treatment with 4-nitrophenyl chloroformate in the presence of pyridine in THF. Yields for these two steps typically ranged from 50 -90 %. These azido 4-nitrophenyl carbamate monomers are reactive enough for coupling and yet stable enough for purification on silica gel column chromatography.



Scheme 1.

Synthesis of an oligourea on support was initiated by coupling a monomer (0.5 mmol) to the free amine of Rink resin[8] (0.1 mmol) in the presence of diisopropylethylamine (DIEA, 0.7 mmol) in CH_2Cl_2 (7 mL) as shown in Scheme 2. Upon addition of the monomer to resin, the solution turned yellow, indicative of the release of 4-nitrophenol and the reaction was completed within 4 h at room temperature. Reduction of the azide group was achieved by sequential addition of triethylamine (TEA, 25 mmol), thiophenol (20 mmol) and $SnCl_2$ (5 mmol) to the suspended resin (1 mmol) in THF (5 mL) and was rapid (< 2 h) at room temperature.[5] Acid labile side-chain protecting groups such as *t*-Boc on lysine and *t*-butyl ether on serine and tyrosine remain intact. Quantitative Kaiser ninhydrin tests[9] indicate that both the coupling and reduction steps proceed in quantitative yield.



Scheme 2.

Cleavage of the oligomers from the support and complete side-chain deprotection was accomplished by a low/high cleavage procedure[10] using 10% trifluoroacetic acid (TFA) in CH_2Cl_2 followed by treatment with 90% TFA-H_2O. Crude material after concentration *in vacuo* was dissolved in EtOAc and precipitated into *t*-

butylmethyl ether to afford 75 to 94% yields of the oligomers. In general, the ether precipitated oligomers were pure enough for analytical purposes (Figure 1).

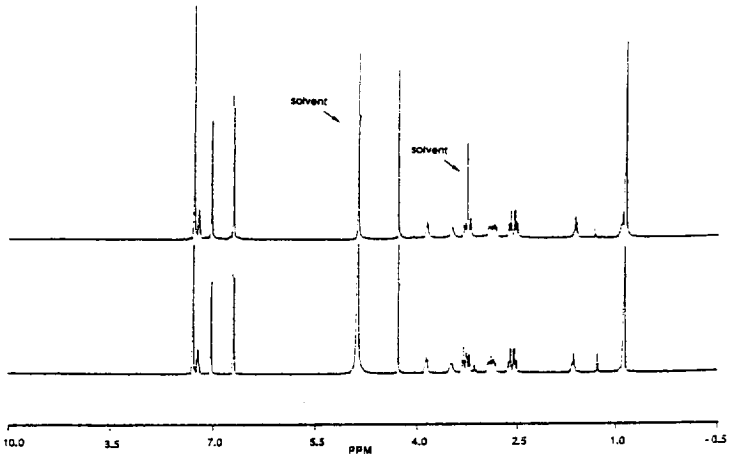
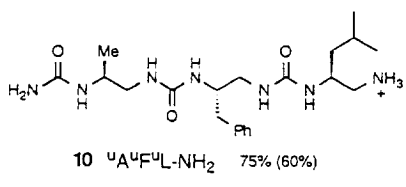
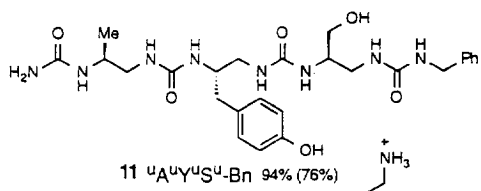


Figure 1. ^{1}H NMR (400 MHz, CD_3OD, 25 °C) spectrum of **12** after *t*-butylmethyl ether precipitation (above) and after HPLC purification (below).

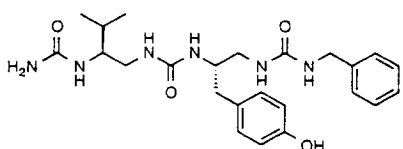
Further purification was performed on C_{18} reverse-phase HPLC (5-100% B over 60 min, A: 0.1% TFA-H_2O; B: 0.08% TFA-MeCN). Using these methods, four oligomers **10-13** have been synthesized with yields, after HPLC purification, ranging from 54 to 76% .



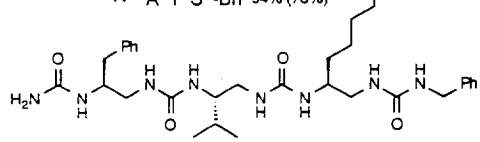
10 $^{u}A^{u}F^{u}L$-NH_2 75% (60%)



11 $^{u}A^{u}Y^{u}S^{u}$-Bn 94% (76%)



12 $^{u}V^{u}Y^{u}$-Bn 91% (57%)



13 $^{u}F^{u}V^{u}K^{u}$-Bn 85% (54%)

In summary, we have described an efficient method for solid phase synthesis of the oligoureas from readily prepared optically active azido 4-nitrophenyl carbamate monomers. Efforts toward the synthesis of a urea combinatorial library and larger folded ureas are under way.

Acknowledgment. We are grateful for financial support for this work from the Office of Naval Research (grant no. N00014-93-1-0380) and by the Director, Office of Energy Research, office of Basic Energy Sciences, Division of Material Sciences, and also by the Division of Energy Biosciences of the U.S. Department

of Energy under Contract No. DE-AC03-76SF00098. PGS is an Howard Hughes Medical Institute Investigator. JMK is an Howard Hughes Medical Institute Associate.

References and Notes.

1. (a) Raleigh, D.P.; Betz, S.F.; DeGrado, W.F. *J. Am. Chem. Soc.* **1995**, *117*, 7558. (b) Quinn, T.P.; Tweedy, N.B.; Williams, R.W.; Richardson, J.S.; Richardson, D.C. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 8747. (c) Harbury, P.B.; Zhang, T.; Kim, P.S.; Alber, T. *Science*, **1993**, *262*, 1401. (d) Desjarlais, J.R.; Handel, T.M. *Protein Sci.* **1995**, *4*, 2006.
2. (a) Lowe, G. *Chem. Soc. Rev.* **1995**, 309. (b) Gallop, M.A.; Barret, R.W.; Dower, W.J.; Fodor, S.P.A.; Gordon, E.M. *J. Med. Chem.* **1994**, *37*, 1233. (c) Lam, K.S.; Salman, S.E.; Hersh, E.M.; Hruby, V.J.; Kazmierski, W.M.; Knapp, R.J. *Nature*, **1991**, *354*, 82 (d) Houghten, R.A.; Pinilla, C.; Blondelle, S.E.; Appel, J.R.; Dooley, C.T.; Cuervo, J.H. *Nature* **1991**, *354*, 84. (e) Fodor, S.P.A.; Read, J.L.; Pirrung, M.S.; Stryer, L.; Lu, A.T.; Solas, D. *Science*, **1991**, *251*, 767.
3. (a) For a recent review: Liskamp, R.M.J. *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 633. (b) Zuckermann, R.N.; Kerr, J.M.; Kent, S.B.H.; Moos, W.H. *J. Am. Chem. Soc.* **1992**, *114*, 10646. (c) Cho, C.Y.; Moran, E.J.; Cherry, S.R.; Stephans, J.; Fodor, S.P.A.; Adams, C.A.; Sundaram, A.; Jacobs, J.W.; Schultz, P.G. *Science* **1993**, *261*, 1303. (d) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2067. (e) Gennari, C.; Nestler, H.P.; Salom, B.; Still, W.C. *Angew. Chem. Int. Ed.* **1995**, *34*, 1763 and 1765. (f) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539. (g) Moree, W. J.; van der Marel, G. A.; Liskamp, R. J.*J. Org. Chem.* **1995**, *60*, 5157.
4. Burgess, K.; Linthicum, D.S.; Shin, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 907.
5. Kick, E. K.; Ellman, J. A. *J. Med Chem.* **1995**, *38*, 1427.
6. Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron lett.* **1991**, *32*. 923.
7. *N*-α-Cbz(benzyloxycarbonyl) protected amino acid was reduced to the corresponding amino alcohol by the procedures described in reference 6. Cbz protecting group was removed by hydrogenation with 10% Pd-C to provide the desired amino alcohol in 90-95% yield for two steps.
8. Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787.
9. Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147.
10. Novabiochem: General Catalog **1992/93**, pp. 104 -121.
11. Spectrascopic data for oligoureas synthesized on solid-support is as follows:

^{u}A^{u}F^{u}LCH$_2$NH$_2$ 10: Cleavage of 0.029 mmol resin gave 9.7 mg (60%) of **10** after HPLC purification. ^{1}H NMR (400 MHz, CD_3OD) δ = 0.91 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.21 - 1.39 (m, 2 H), 1.69 (m, 1 H), 2.51 - 2.67 (m, 4 H), 2.75 (dd, J = 14.0, 5.2 Hz, 1 H), 3.05 (dd, J = 12.8, 3.0 Hz, 1 H), 3.20 (dd, J = 13.9, 4.2 Hz, 1 H), 3.54 (dd, J = 14.0, 3.3 Hz, 1 H), 3.78 (m, 1 H), 4.03 (m, 1 H), 4.19 (m, 1 H), 7.14 - 7.26 (m, 5 H); ^{13}C NMR (100 MHz, D_2O, CH_3OH as reference) δ = 17.8, 21.2, 22.6, 24.4, 38.6, 41.2, 44.4, 44.7, 45.2, 46.7, 52.1, 126.8, 128.8, 129.6, 138.7, 160.4, 160.5, 161.2; FABMS m/z (relative intensity) 436 (M+1, 100), 177 (40), 117 (76); HRMS (FAB) m/z 436.3040 ($C_{21}H_{38}N_7O_3$ requires 436.3036).

^{u}A^{u}Y^{u}S^{u}CH$_2$Ph 11: Cleavage of 0.093 mmol resin gave 39.5 mg (76%) of **11** after HPLC purification. ^{1}H NMR (400 MHz, CD_3OD) δ = 0.99 (d, J = 6.7 Hz, 3 H), 2.50 (dd, J = 13.9, 8.1 Hz, 1 H), 2.58 - 2.78 (m, 3 H), 3.0 (m, 1 H), 3.8 (m, 1 H), 3.42 - 3.57 (m, 4 H), 3.77 (m, 2 H), 3.96 (m, 1 H), 4.30 (s, 2 H), 6.65 (d, J = 8.4 Hz, 2 H), 6.95 (d, J = 8.4 Hz, 2 H), 7.19 - 7.28 (m, 5 H); ^{13}C NMR (100 MHz, CD_3OD) δ = 18.8, 39.2, 42.4, 44.7, 45.4, 47.1, 47.2, 52.7, 53.2, 63.6, 116.1, 127.9, 128.2, 129.5, 130.3, 131.2, 141.3, 156.8, 161.1, 161.3, 161.5, 161.9; FABMS m/z (relative intensity) 559 (M+1, 3), 460 (3), 307 (26), 154 (100); HRMS (FAB) m/z 559.2999 ($C_{26}H_{39}N_8O_6$ requires 559.2993).

^{u}V^{u}Y^{u}CH$_2$Ph 12: Cleavage of 0.064 mmol resin gave 17.1 mg (57%) of **12** after HPLC purification. ^{1}H NMR (400 MHz, CD_3OD) δ = 0.86 (d, J = 5.0 Hz, 3 H), 0.88 (d, J = 4.9 Hz, 3 H), 1.67 (m, 1 H), 2.59 (dd, J = 13.9, 7.5 Hz, 1 H), 2.67 (dd, J = 13.9, 6.2 Hz, 1 H), 2.90 (dd, J = 13.5, 9.1 Hz, 1 H), 2.96 (dd, J = 13.1, 7.6 Hz, 1 H), 3.26 (dd, J = 13.9, 5.4 Hz, 1 H), 3.35 (dd, J = 13.5, 4.5 Hz, 1 H), 3.52 (br s, 1 H), 3.90 (m, 1 H), 4.30 (s, 2 H), 6.68 (d, 8.5 Hz, 2 H), 7.01 (d, 8.5 Hz, 2 H), 7.19 - 7.30 (m, 5 H); ^{13}C NMR (100 MHz, CD_3OD) δ = 18.0, 20.0, 31.6, 39.2, 43.7, 44.7, 44.9, 53.3, 56.4, 116.1, 127.9, 128.2, 129.5, 130.3, 131.6, 141.3, 156.9, 161.0, 161.3, 162.4; FABMS m/z (relative intensity) 471 (M+1, 19), 154 (100), 136 (78), 107 (32); HRMS (FAB) m/z 471.2724 ($C_{24}H_{35}N_6O_4$ requires 471.2720).

^{u}F^{u}V^{u}K^{u}CH$_2$Ph 13: Cleavage of 0.070 mmol resin gave 27.4 mg (54 %) of **13** after HPLC purification. ^{1}H NMR (400 MHz, CD_3OD) δ = 0.80 (d, J = 3.2 Hz, 3 H), 0.81 (d, J = 3.3 Hz, 3 H), 1.28 (m, 1 H), 1.40 (m, 3 H), 1.65 (m, 3 H), 2.51 (m, 4 H), 2.86 (m, 3 H), 3.43 (dd, J = 14.1, 3.6 Hz, 1 H), 3.60 (m, 3 H), 3.75 (m, 1 H), 4.05 (m, 1 H), 4.34 (ABq, J = 15.3 Hz, 2 H), 7.14 - 7.33 (m, 10 H); ^{13}C NMR (100 MHz, CD_3OD) δ = 18.2, 20.0, 23.7, 28.0, 31.8, 33.5, 39.9, 40.6, 44.6, 44.7, 45.5, 46.4, 51.1, 52.4, 56.1, 127.3, 127.9, 128.4, 129.4, 129.5, 130.2, 139.8, 141.4, 161.2, 161.6, 161.8, 161.9; FABMS m/z (relative intensity) 612 (M+1, 100), 305 (66); HRMS (FAB) m/z 612.3984 ($C_{31}H_{50}N_9O_4$ requires 612.3986).

(*Received in USA* 10 *May* 1996; *accepted* 30 *May* 1996)