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Synthesis of a Cyclic Urea as a Nonnatural Biopolymer Scaffold

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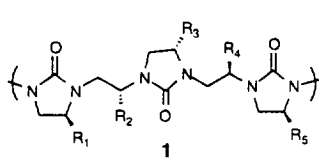
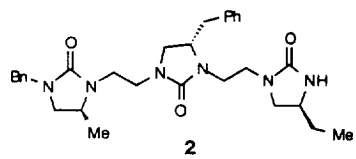
Abstract: A cyclic urea trimer was synthesized from readily available amino acid derivatives using a simple, iterative approach. A selective amide reduction using borane (BH_3-THF) and a triphosgene-mediated cyclization are the key features in a synthesis of the cyclic urea trimer **2**. Copyright © 1996 Elsevier Science Ltd

Peptides are attractive targets for drug discovery because of their high affinities and specificities toward biological receptors and the ease with which large peptide libraries can be synthesized in a combinatorial format. The screening of peptide libraries has led to the identification of numerous, biologically-active peptide leads.[1] However, the poor stability and bioavailibility of peptides *in vivo* have generally limited their therapeutic application.[2] One approach toward overcoming this obstacle has been the development of non-natural biopolymer scaffolds with improved pharmacological properties relative to peptides.[3] As a part of our efforts to develop non-natural biopolymers, we have begun to investigate the synthesis of oligomeric cyclic ureas (**1**). Cyclic urea moieties are found in many biologically active compounds,[4] and are expected to have greater membrane solubility and increased conformational rigidity relative to the corresponding linear urea. We now report a facile synthesis of the simple cyclic urea trimer **2** (R_1= Me, R_2= H, R_3= Bn, R_4= H, R_5= Et).

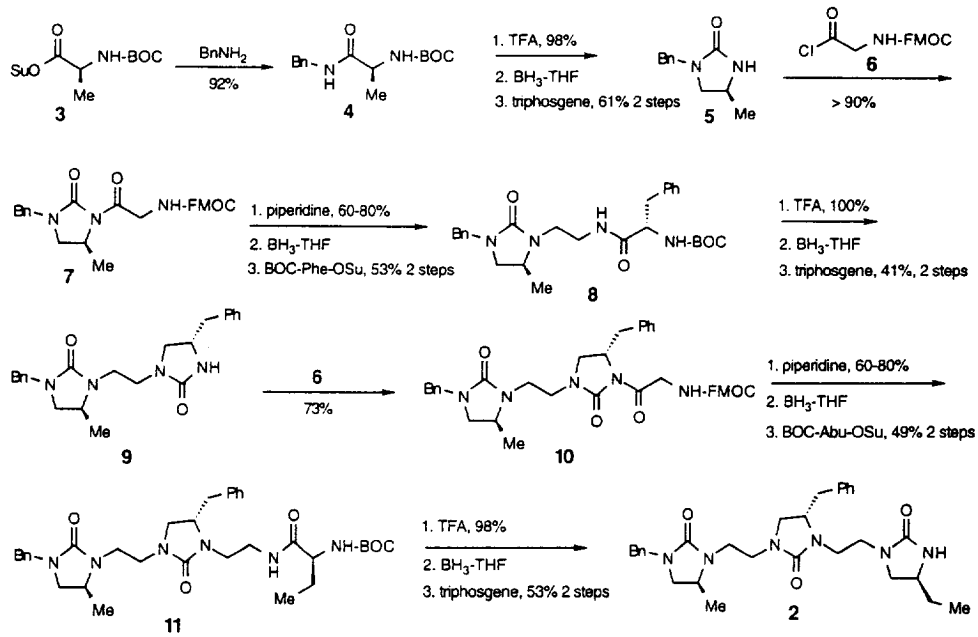


1



2

An iterative approach was employed for the synthesis of the cyclic oligourea **2** (Scheme **1**). Coupling of BOC-alanine *N*-hydroxysuccinimide ester **3** with benzylamine provided amide **4** in high yield (CH_2Cl_2, 25 °C, 18 h). Subsequent removal of the BOC protecting group (TFA, CH_2Cl_2, 25 °C, 1 h), amide reduction with BH_3-THF (THF, reflux, 22 h), and cyclization with triphosgene (CH_2Cl_2, 25 °C, 16 h) gave the cyclic urea **5**.



Scheme 1.

Cyclic urea **5** was cleanly acylated in nearly quantitative yield by treatment with FMOC-glycine acid chloride **6**[5a] and the sterically hindered base 2,6-di-*t*-butyl-4-methylpyridine (CH_2Cl_2, 25 °C, 4 h). Similar reactions using diisopropylethylamine (DIEA) or triethylamine (TEA) resulted in a lower yield (< 50%) of **7**, presumably because DIEA and TEA convert the acid chloride **6** into the less reactive oxazolone.[5b] Removal of the FMOC protecting group with piperidine (CH_2Cl_2, 25 °C, 1 h), followed by reduction with borane BH_3-THF (THF, 60 °C, 3 h) and coupling with BOC-Phe-OSu (CH_2Cl_2, 25 °C, 2.5 h) provided **8**. Proton and carbon NMR analysis of the crude mixture after work-up (1M HCl-MeOH, 25 °C, 1 h) indicated that the amide was cleanly reduced to the corresponding amine in the presence of the cyclic urea moiety. Reaction conditions used to convert **8** to the cyclic urea dimer **9** were similar to those employed to prepare the cyclic-urea **5** from **4** as shown in Scheme **1**. Addition of another cyclic urea moiety to dimer **9** was achieved by repeating the reaction conditions from previous steps to afford trimer **2**. All yields indicated represent isolated yields of pure intermediates and satisfactory spectroscopic and analytical data was obtained for all new compounds.[6]

In summary, we have described a simple, iterative method for the synthesis of the cyclic urea trimer **2** from readily available amino acid derivatives using a selective borane reduction and triphosgene promoted cyclization. Preliminary experiments on borane reduction and triphosgene cyclization have been promising, and efforts toward incorporating this chemistry into a solid-phase synthetic approach are currently underway.

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6. ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (70 MHz) were recorded on $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to TMS or $CHCl_3$. Melting points (Pyrex capillary) are uncorrected. Compounds are oils unless melting points are specified.

   4: white powder (mp: 100-102 °C); ^{1}H NMR 1.37 (d, J = 7.1 Hz, 3H), 1.40 (s, 9H), 4.23 (br s, 1H), 4.41 (br s, 2H), 5.20 (br s, 1H), 6.83 (br s, 1H), 7.25 (m, 5H); ^{13}C NMR 18.4, 28.2, 43.3, 50.1, 80.0, 127.3, 127.5, 128.6, 138.1, 155.5, 172.6; FABMS m/z (relative intensity) 279 (M+1, 53), 223 (94), 179 (100), 106 (53); HRMS (FAB) m/z 279.1707 ($C_{15}H_{23}N_2O_3$ requires 279.1709)

   5: white powder (mp: 82-84 °C); ^{1}H NMR 1.20 (d, J = 6.2 Hz, 3H), 2.83 (dd, J = 8.6, 6.4 Hz, 1H), 3.39 (t, J = 8.6 Hz, 1H), 3.75 (m, 1H), 4.35 (ABq, J = 15.0 Hz, 2H), 7.25 (m, 5H); ^{13}C NMR 21.4, 45.4, 47.3, 51.6, 127.2, 127.9, 128.5, 137.1, 162.0; FABMS m/z (relative intensity) 191 (M+1, 100), 113 (9); HRMS (FAB) m/z 191.1186 ($C_{11}H_{15}N_2O_1$ requires 191.1184)

   7: white powder (mp: 60-65 °C); ^{1}H NMR 1.31 (d, J = 6.4Hz, 3H), 2.88 (dd, J = 9.2, 2.5 Hz, 1H), 3.49 (t, J = 9.0Hz, 1H), 4.25-4.53 (m, 6H), 4.59 (dd, J = 19.1, 5.3 Hz, 1H), 4.68 (dd, J = 19.1, 5.7 Hz, 1H), 5.56 (br t, 1H), 7.26-7.43 (m, 9H), 7.64 (d, J = 7.3 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H); ^{13}C NMR 20.0, 45.3, 47.1, 47.2, 47.5, 48.7, 67.0, 119.8, 125.1 , 127.0, 127.6, 128.0, 128.1, 128.8, 135.4, 141.2,

143.8, 143.9, 154.0, 156.3, 169.2; FABMS m/z (relative intensity) 470 (M+1, 4), 248 (10), 231 (28), 191 (34), 179 (100), 165 (18), 133 (8); HRMS (FAB) m/z 470.2091 ($C_{28}H_{28}N_3O_4$ requires 470.2080)

8: white powder (mp: 40-45 °C); ^{1}H NMR 1.18 (d, J = 6.0 Hz, 3H), 1.38 (s, 9H), 2.72 (t, J = 8.3 Hz, 1H), 3.09 (br s, 1H), 3.10 (dd, J = 13.8, 6.2 Hz, 1H), 3.20-3.42 (m, 5H), 3.58 (m, 1H), 4.32 (ABq, J = 14.9 Hz, 2H), 4.38 (br s, 1H), 5.12 (d, J = 7.5 Hz, 1H), 6.90 (br s, 1H), 7.19-7.32 (m, 10H); ^{13}C NMR 18.7, 28.2, 38.7, 39.2, 41.0 55.6, 79.7, 126.6, 127.4, 128.0, 128.4, 128.5, 129.3, 136.8, 136.9, 155.2, 161.4, 171.6; FABMS m/z (relative intensity) 481 (M+1, 14), 381 (100), 234 (59), 217 (52), 120 (50); HRMS (FAB) m/z 481.2823 ($C_{27}H_{37}N_4O_4$ requires 481.2815)

9: ^{1}H NMR 1.21 (d, J = 6.2 Hz, 3H), 2.69-2.77 (m, 2H), 2.85 (dd, J = 12.4, 5.6 Hz, 1H), 2.95-3.11 (m, 2H), 3.37 (t, J = 8.5 Hz, 1H), 3.48 (t, J = 8.6 Hz, 1H), 3.55 (dd, J = 8.6, 5.2 Hz, 1H), 3.65-3.90 (m, 4H), 4.34 (s, 1H), 4.38 (ABq, J = 15.1 Hz, 2H), 7.17-7.32 (m, 10H); ^{13}C NMR 18.2, 38.0, 40.3, 41.8 47.6 , 47.9, 49.6, 50.0, 51.1, 126.5, 127.1, 127.8, 128.4, 128.5, 129.1, 137.2, 137.3, 160.6, 161.3; FABMS m/z (relative intensity) 393 (M+1, 100), 301 (7), 217 (18), 203 (21), 117 (8); HRMS (FAB) m/z 393.2293 ($C_{23}H_{28}N_4O_2$ requires 393.2291)

10: ^{1}H NMR 1.21 (d, J = 6.1 Hz, 3H), 2.72 (m, 2H), 2.92 (m, 1H), 3.08 (m, 1H), 3.22 (d, J = 10.5 Hz, 1H), 3.30 (t, J = 9.0 Hz, 1H), 3.36 (t, 8.5 Hz, 1H), 3.50 (dd, J = 9.1, 2.0 Hz, 1H), 3.66-3.82 (m, 3H), 4.26 (t, J = 7.6 Hz, 2H), 4.41-4.62 (m, 5H), 5.63 (br t, 1H), 7.20-7.46 (m, 14H), 7.64 (d, J = 5.8 Hz, 2H), 7.76 (d, J = 7.5 Hz, 2H); 13C NMR 18.3, 37.9, 40.9, 45.3, 45.8, 47.1, 47.9, 50.0, 52.6, 67.0, 119.9, 125.1, 126.8, 127.0, 127.3, 127.6, 127.9, 128.5, 128.6, 129.7, 136.5, 137.1, 141.2, 143.9, 144.0, 154.4, 156.3, 160.6, 169.1; FABMS m/z (relative intensity) 672 (M+1, 56), 393 (24), 154 (100); HRMS (FAB) m/z 672.3187 ($C_{40}H_{42}N_5O_5$ requires 672.3186)

11: ^{1}H NMR 0.89 (t, J = 7.4 Hz, 3H), 1.20 (d, J = 6.1 Hz, 3H), 1.41 (s, 9H), 1.61 (m, 1H), 1.82 (m, 1H), 2.65 (dd, J = 13.2, 9.5 Hz, 1H), 2.71 (t, J = 8.1 Hz, 1H), 2.95-3.08 (m, 3H), 3.16-3.23 (m, 3H), 3.32-3.71 (m, 6H), 3.76-3.85 (m, 2H), 4.05 (m, 1H), 4.26 (d, J = 15.1 Hz, 1H), 4.44 (d, J = 15.1 Hz, 1H), 5.22 (br d, 1H), 7.10 (br s, 1H), 7.21-7.23 (m, 10H); ^{13}C NMR 9.7, 18.3, 26.3, 28.3, 38.2, 39.0, 39.1, 41.1, 41.5, 47.9, 48.0, 50.2, 55.3, 55.6, 79.5, 126.7, 127.3, 127.9, 128.5, 128.7, 129.3, 136.7, 137.3, 155.4, 160.6, 161.4, 172.2; FABMS m/z (relative intensity) 621 (M+1, 7), 521 (100); HRMS (FAB) m/z 621.3748 ($C_{34}H_{49}N_6O_5$ requires 621.3764)

2: ^{1}H NMR 0.88 (t, J = 7.4 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.50 (m, 2H), 2.62 (dd, J = 13.2, 9.2 Hz, 1H), 2.69 (t, J = 8.0 Hz, 1H), 2.89-3.04 (m, 5H), 3.15 (t, J = 8.7 Hz, 1H), 3.28 (dd, J = 8.5, 6.1 Hz, 1H), 3.32-3.36 (m, 2H), 3.43 (t, J = 8.5 Hz, 1H), 3.52-3.86 (m, 6H), 3.98 (m, 1H), 4.24 (d, J = 15.1 Hz, 1H), 4.49 (d, J = 15.1 Hz, 1H), 4.62 (s, 1H), 7.21-7.32 (m, 10H); ^{13}C NMR 9.5, 18.2, 28.5, 38.3, 38.6, 38.7, 40.6, 41.0, 47.7, 47.8, 48.0, 49.8, 50.2, 51.2, 53.4, 126.5, 127.2, 127.8, 128.5, 128.6, 129.4, 137.1, 137.4, 160.3, 160.6, 161.7; FABMS m/z (relative intensity) 533 (M+1, 100), 441 (20), 217 (36); HRMS (FAB) m/z 533.3235 ($C_{30}H_{41}N_6O_3$ requires 533.3240)

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