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Synthesis of small cyclic peptides constrained with 3-(3-aminomethylphenyl)propionic acid linkers using free radical-mediated macrocyclization☆

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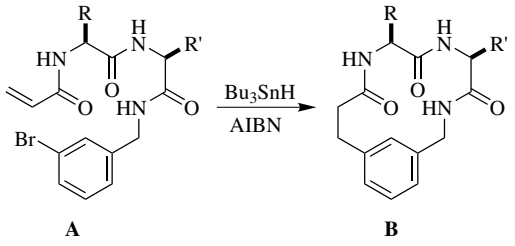
Abstract—In this letter, we report that small peptides (di- and tri-) having a 3-bromobenzyl group at the C-termini and an acryloyl group at the N-termini undergo an efficient Bu_3SnH–AIBN mediated intramolecular free radical cyclization to afford cyclic peptides in good yields. We also propose that these cyclizations are occurring via a pre-organized acyclic structure dictated by a reverse turn (γ/β-turn).

Radical reactions offer excellent protocols desired by the synthetic organic chemist in terms of mildness, variety and potential for C–C bond formation as well as for functional group interconversions.[1] The construction of small rings using free radical chemistry is well documented in the literature, however there are limited protocols available for the synthesis of large rings using free radical-mediated macrocyclizations.[2] In these reports, activation of the olefin as an acrylate ester allows the preparation of larger rings (e.g., 12–20 members) through Bu_3SnH–AIBN free radical-mediated cyclization in good yield. In this macrocyclization, *endo* cyclization is favored.[2]

As part of an ongoing program in our laboratory on peptidomimetics,[3,4] we are interested in the synthesis of di- and tri-peptides constrained with disubstituted aromatic linkers for conformational and binding studies. Towards this goal, we designed a macrocycle containing a constrained dipeptide with the 3-(3-aminomethylphenyl)propionic acid linker. We envisioned the preparation of our desired macrocycle (**B**) from the corresponding acyclic precursor (**A**) through a free radical-mediated cyclization (Scheme 1).



Scheme 1.

Preliminary results indicated that macrocycles were obtained in good yields when free radical chemistry was attempted on appropriate precursors. In this letter, we show that radical-mediated macrocyclizations can be used for the synthesis of cyclic peptides. To the best of our knowledge, this is the first report on the use of aryl radical-mediated macrocyclization for the synthesis of cyclic peptides.

For the construction of the acyclic precursor **3a**, Leu-OMe was coupled with *N*-Boc-Phe-OH **1a** following a standard protocol for peptide coupling using isobutyl chloroformate as the coupling reagent. After ester hydrolysis (LiOH/MeOH) the resulting dipeptide coupling with 3-bromobenzylamine gave **2a**, which on Boc deprotection (TFA/DCM), followed by acylation with acryloyl chloride (Et_3N/CH_2Cl_2), gave the desired compound **3a** in a satisfactory overall yield. The compound

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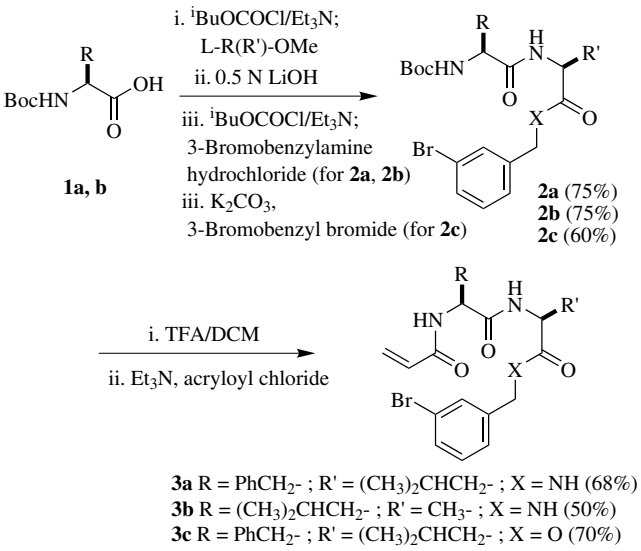
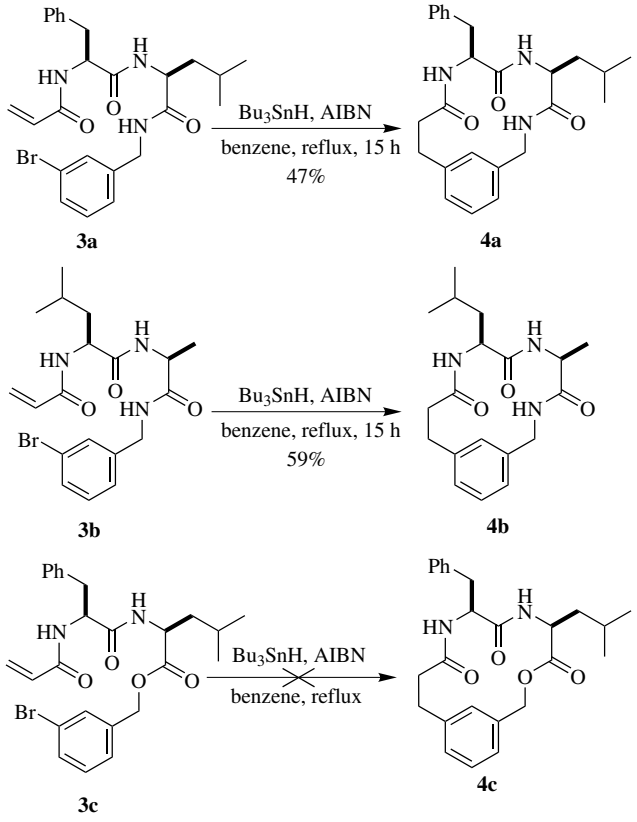


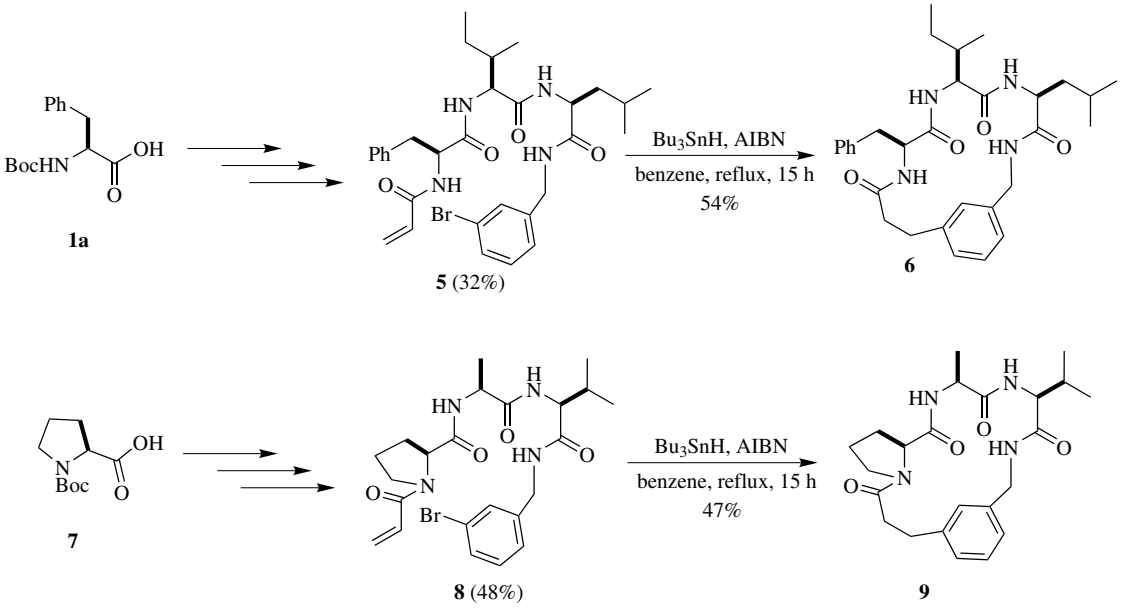
Scheme 2.

N-Boc-Leu-OH **1b** was coupled with L-Ala-OMe with ester hydrolysis, followed by reaction with 3-bromobenzylamine to produce **2b** in good yield. Deprotection of the Boc group, followed by acylation with acryloyl chloride resulted in **3b**. We essentially followed the same procedure as that of **3a** for the synthesis of the oxygen analogue **3c**, except that 3-bromobenzylamine was replaced by 3-bromobenzyl bromide (Scheme 2).

Having acyclic precursors **3a–c** in hand for the key step, we subjected them to an intramolecular free radical reaction using Bu$_3$SnH–AIBN in dry benzene or acetonitrile to give the corresponding cyclic peptides.[5] To our delight, **3a** and **3b** underwent smooth cyclization to furnish the cyclic peptides **4a** and **4b**. Compounds **4a** and **4b** were purified by column chromatography (230–400 mesh silica gel/MeOH:DCM) and characterized by NMR and mass spectroscopy.[5] High dilution ^{1}H NMR studies[6] indicated the presence of an intramolecular hydrogen bond in the cyclic peptides, suggesting that these cyclic structures organized through a γ/β-turn. However, in the case of acyclic peptide **3c** the Bu$_3$SnH–AIBN mediated free radical cyclization failed to give the corresponding cyclic peptide **4c** despite many attempts (Scheme 3). Based on these experimental results, we



Scheme 3.



Scheme 4.

propose that compounds **3a** and **3b** are pre-organized structures through intramolecular H-bonding (γ/β-turn) of the benzylic NH with the *i* or *i*+1 amino acid carbonyl group, which is not possible in the case of the corresponding oxygen analogue **3c**.[7] The pre-organization by a reverse turn may bring the two reacting partners closer to each other, thereby resulting in a facile ring closure. The lack of an intramolecular hydrogen bond (γ/β-turn) for the pre-organized structure in compound **3c** explains the observed cyclization results.

Encouraged by the success with the dipeptide-cyclization, we explored the versatility of this intramolecular free radical reaction in tripeptide-cyclization. For the preparation of macrocycles **6** and **9**, the corresponding acyclic compounds **5** and **8** were prepared from Boc-Phe-OH **1a** and Boc-Pro-OH **7** following the same procedure described for the synthesis of dipeptides **3a**–**c**, respectively.[8] The acyclic compounds **5** and **8** were subjected to the Bu_3SnH–AIBN mediated intramolecular free radical reaction in dry benzene resulting in smooth cyclization to furnish the corresponding cyclic peptides **6** and **9**, respectively (Scheme 4).

In short, we have developed an efficient protocol for the synthesis of cyclic peptides constrained with the 3-(3-aminomethylphenyl)propionic acid linker using a Bu_3SnH–AIBN mediated intramolecular free radical reaction. We also propose that these macrocyclizations are controlled by the presence of an intramolecular H-bond (γ/β-turn) in the acyclic precursors and the cyclic peptides. These cyclic peptides may be useful probes in understanding the role of constrained structures in the search for bioactive conformations in larger proteins.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.115.

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5. Representative procedure for free radical cyclization: To a refluxing solution of 3-bromobenzyl-*N*-acryloyl-L-Phe-L-leucine amide **3a** (0.150 g, 0.3 mmol) in dry benzene (300 mL) and 2,2′-azobisisobutyronitrile (cat) was added tri-*n*-butyltin hydride (0.097 mL, 0.36 mmol) very slowly, 0.5 mL/h. The reaction mixture was refluxed for 15 h. Then benzene was evaporated and the crude compound was purified by column chromatography (230–400 silica gel, CH_3OH/CH_2Cl_2 2.0/98.0) to yield the product **4a** as a white solid (0.06 g, 47%), mp 305–306 °C; $[\alpha]_D$ −103.0 (*c* 0.1, DMSO); IR (KBr): 3297, 2926, 1650 cm^{-1}; ^1H NMR (DMSO-*d*6 + $CDCl_3$, 400 MHz) δ 8.45 (t, *J* = 5.91 Hz, 1H), 8.02 (d, *J* = 8.33 Hz, 1H), 7.82 (d, *J* = 8.59 Hz, 1H), 7.29–7.12 (m, 6H), 7.02–6.99 (m, 2H), 6.86 (s, 1H), 4.43–4.34

(m, 2H), 4.17 (q, J = 7.52 Hz, 1H), 4.00 (dd, J_1 = 5.37 Hz, J_2 = 15.31 Hz, 1H), 3.10–3.04 (m, 1H), 2.95–2.83 (m, 2H), 2.66–2.60 (m, 1H), 2.36–2.33 (m, 2H), 1.56–1.49 (m, 2H), 1.35 (sept, J = 7.71 Hz, 1H), 0.89 (d, J = 6.71 Hz, 3H), 0.86 (d, J = 6.71 Hz, 3H); ^{13}C NMR (DMSO-*d*6, 50 MHz) δ 171.5, 171.3, 171.1, 141.8, 139.5, 137.4, 129.1, 128.8 (2C), 128.2 (2C), 127.7, 127.2, 126.4, 124.9, 124.2, 56.1, 52.1, 41.5, 36.7, 35.1, 29.1, 24.3, 22.5, 22.2; MS (CI) *m*/*z* 422 (M^++1, 100%).

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7. Although, we proposed a reverse turn in **3a** and **3b** based on experimental results, we could not confirm the presence of the H-bond using NMR studies.
8. See experimental details in the Supporting information.