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Synthesis of small cyclic peptides via intramolecular Heck reactions

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Abstract—Tripeptides having a 3-bromobenzyl group at the C-termini and an acryloyl group at the N-termini undergo efficient intramolecular Heck reactions to afford the corresponding cyclic peptides in good yields. Synthesis of two such peptides is discussed. © 2002 Published by Elsevier Science Ltd.

Rational drug design based on protein targeting requires the understanding of the bound conformation of bioactive peptides.[1] Generally, acyclic peptides are difficult to develop as drugs and this limitation has necessitated the use of small cyclic peptides as potent therapeutic agents in recent years. In addition to circumventing the problems of poor bioavailability and proteolytic degradation, cyclic peptides do not suffer from significant entropic disadvantages and if suitably designed can mimic the 'bioactive conformation' which enhances the affinity of such structures to the target. Small cyclic peptides[2] based on protein turn motifs[3] are attractive mimics of the 'bioactive conformations' because numerous peptides elicit biological responses via such a conformation. In an ongoing program on the mimicry of helix–turn–helix motifs, we required the synthesis of small cyclic peptides **1** and **2** (Fig. 1), having an aromatic ring linker, for conformational and binding studies. This paper describes our initial studies which demonstrate that intramolecular Heck reactions[4] can be used in the cyclisation step leading to an efficient synthesis of these cyclic peptides. These cyclisations are accompanied by a concomitant formation of cinnamoyl groups having amino methyl functionality at the 3-position of the aromatic ring.

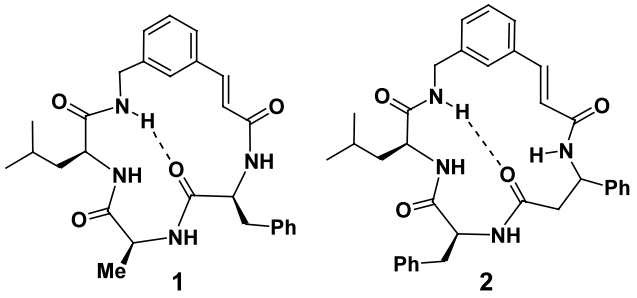

Figure 1. Synthesis of small cyclic peptides.

The synthesis of the cyclic peptide **1** was accomplished by an intramolecular Heck reaction on the tripeptide precursor **8** whose synthesis is described in Scheme 1. The L-*phe*-L-*ala* dipeptide **3** was coupled with L-*leu* methyl ester by standard mixed anhydride protocol[5] to give the corresponding tripeptide **4**, which on base hydrolysis (LiOH–MeOH) afforded the tripeptide acid **5**. The acid **5** was coupled with 3-bromobenzylamine hydrochloride (^{i}BuOCOCl–Et_3N) to give the peptide **6** which on deprotection (CF_3CO_2H–CH_2Cl_2) of *t*-BOC followed by acylation with acryloyl chloride (K_2CO_3/acetone) gave the precursor tripeptide **8** in a satisfactory yield overall. The ^{1}H NMR of the tripeptide **8** in dilute $CDCl_3$ indicated the presence of an intramolecular hydrogen bond suggesting that the molecule may be preorganised via a β-turn.

The tripeptide **8** was subjected to an intramolecular Heck reaction using $Pd(OAc)_2$–(*o*-tolyl)$_3$P–Et$N(^i Pr)_2$ in acetonitrile (0.01 mM solution) for 36 h at 80°C to give the corresponding cyclic peptide **1** which was isolated by column chromatography (silica gel/hexane:ethyl acetate) in 39% yield. The ^{1}H NMR spectrum of **1** revealed the *E*-geometry for the cinnamoyl double bond formed during the cyclisation. High dilution ^{1}H NMR studies[6]

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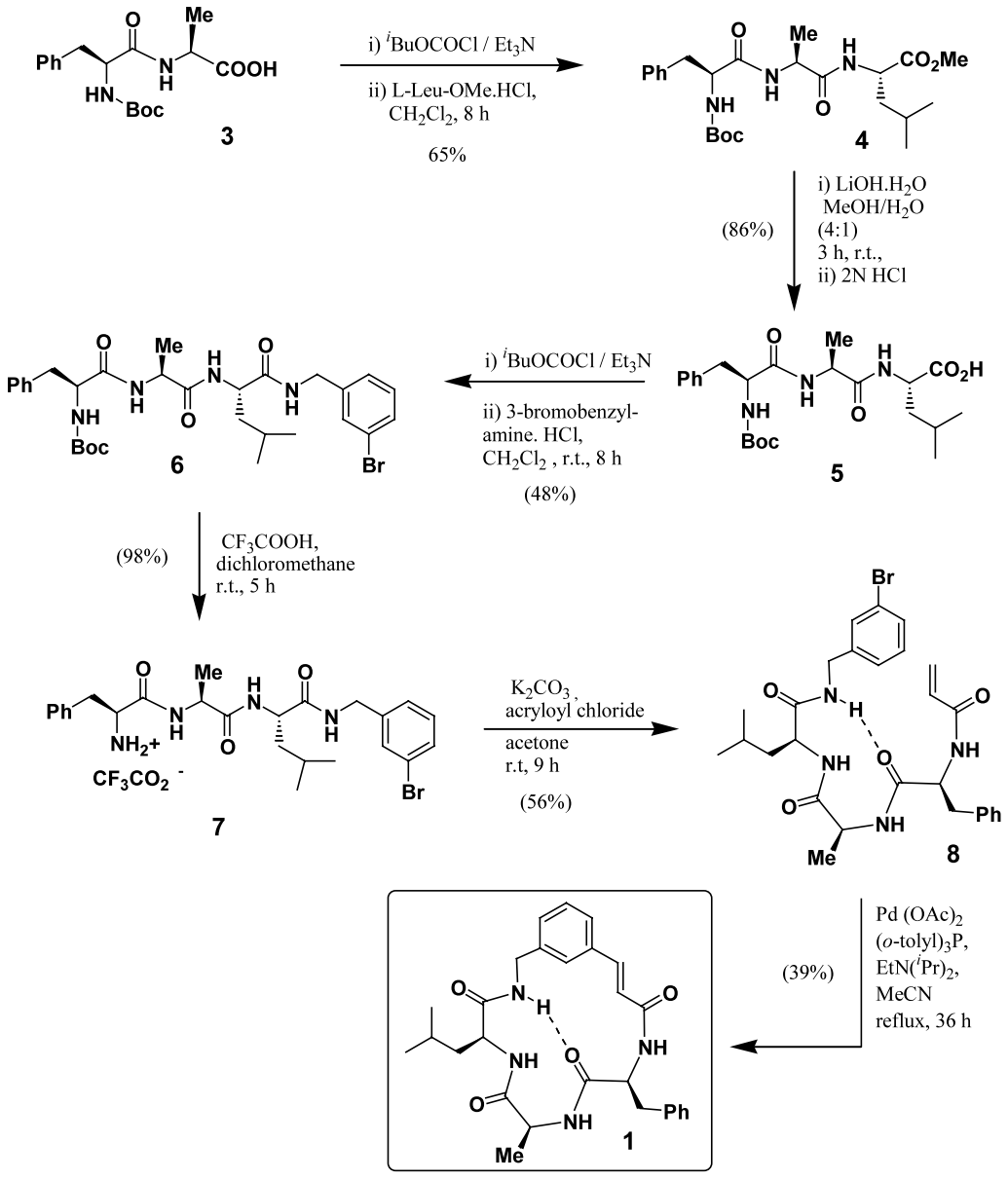
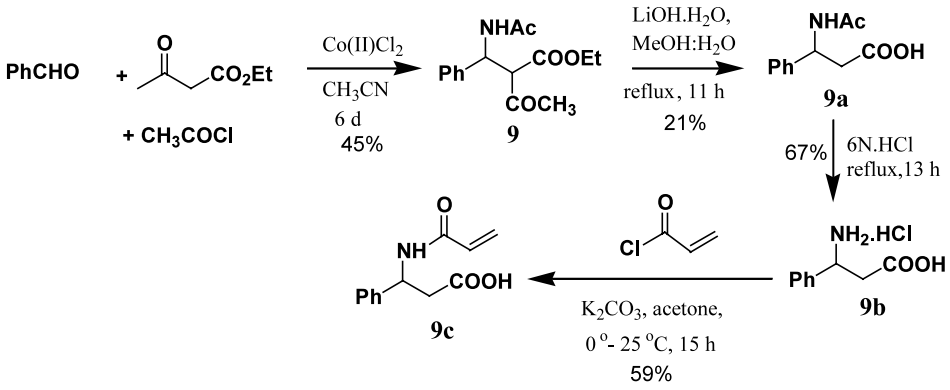


Scheme 1. Synthesis of cyclic peptide **1** by an intramolecular Heck reaction.

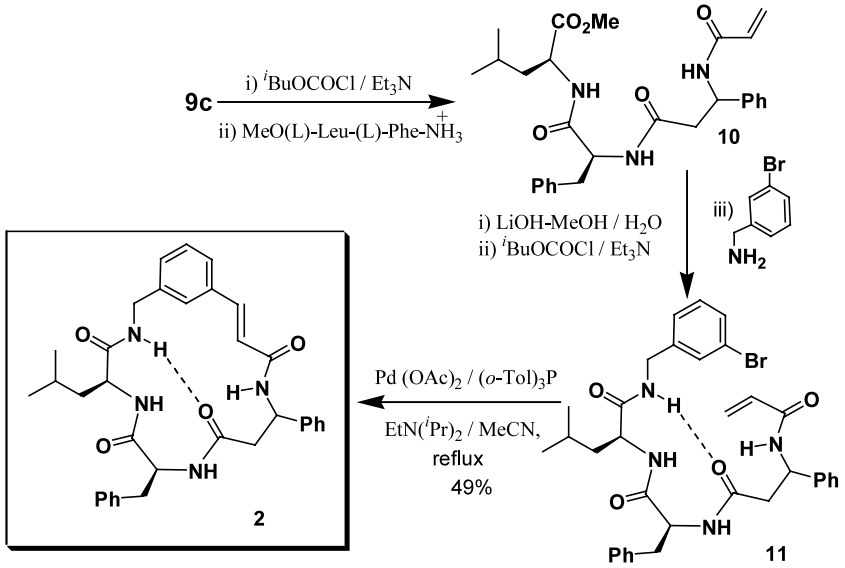
with DMSO-d_6 in $CDCl_3$ indicated the presence of an intramolecular hydrogen bond in the cyclic peptide **1** which appears to exist as a mixture of two conformers in contrast to the acyclic tripeptide precursor **8** which showed the presence of a single species. The versatility of the intramolecular Heck reaction in the synthesis of cyclic peptides was also demonstrated using tripeptides having a β-amino acid. The β-amino acid **9c** was synthesised using a cobalt-catalysed three-component coupling procedure developed by us earlier.[7] The β-acetamido ketone **9** obtained by the cobalt(II) chloride-catalysed three-component coupling was hydrolysed to the corresponding carboxylic acid **9a** which on deacetylation afforded the β-amino acid (homophenylglycine) hydrochloride **9b** (Scheme 2).

The hydrochloride salt **9b** was acylated with acryloyl chloride to afford the corresponding β-phenylglycine derivative **9c**. The β-amino acid **9c** was coupled with MeO(L)-Leu-L-Phe hydrochloride to give the corresponding tripeptide **10** which was hydrolysed and coupled with 3-bromobenzylamine (^{t}BuOCOCl/Et_3N) to give the precursor **11** (Scheme 3).

The ^{1}H NMR of the tripeptide **11** indicated the presence of an intramolecular hydrogen bond in $CDCl_3$ and variable temperature ^{1}H NMR studies supported the above fact. The peptide **11** was subjected to an intramolecular Heck reaction in the presence of $Pd(OAc)_2$–$(o\text{-tolyl})_3P$–$EtN(^iPr)_2$ in acetonitrile (0.01 mM solution) at 80°C and the reaction mixture was worked up and the residue was subjected to column chromatography (silica gel/hexane–EtOAc) to afford the corresponding cyclic peptide **2**[8] in good yield. The *E*-geometry of the double bond of the cinnamoyl group and the presence of an intramolecular hydrogen bond



Scheme 2. Synthesis of a β-amino acid.



Scheme 3. Synthesis of cyclic peptide **2** by an intramolecular Heck reaction.

in **2** was assigned based on ^{1}H NMR. Variable temperature studies on the cyclic peptide **2** confirmed that the β-turn present in the acyclic peptide is also retained in the cyclic peptide **2**. The presence of an intramolecular hydrogen bond also suggests that the molecule is preorganised by a β-turn and this preorganisation may have facilitated the intramolecular Heck reaction. The preorganisation by the β-turn may have brought the two reacting partners closer to each other thereby resulting in a facile ring closure. However, this is just conjuncture and further studies will shed some light on this aspect.

In conclusion, we have developed an efficient protocol for the synthesis of cyclic peptides using intramolecular Heck reactions. These cyclic peptides may be useful probes for DNA–protein interactions and we are currently studying their binding profile with several biomolecules.

Acknowledgements

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4. For a general Heck coupling reaction, see: (a) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083; (b) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133; (c) Patel, B. A.; Ziegler, C. B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. C.; Terpko, M.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3903–3907; (d) Beletskaya, I.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; (e) Grisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427; (f) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, 1998; (g) Link, J. T.; Overman, L. E. *Chemtech.* **1998**, *28*, 19; (h) Negishi, E.; Ma, M.; Sugihara, T.; Noda, Y. *J. Org. Chem.* **1997**, *62*, 1922–1923.
5. **Standard amide coupling procedure**: To an ice-cold stirred solution of the acid (1 equiv.) in dry dichloromethane (5 mL) was added triethylamine (1 equiv.) followed by isobutyl chloroformate (1 equiv.). The resulting mixture was stirred vigorously for 5 min and then the XAA-aminoester. HCl (1 equiv.) was added followed by 2 equiv. of triethylamine. The mixture was stirred for 5 h and washed thoroughly with sodium bicarbonate solution, saturated citric acid solution and water (3×10 mL). Drying and concentration in vacuo yielded the crude peptide which on column chromatography (silica gel, EtOAc:hexane) afforded the desired peptide in good yield. *Spectral data for* ***8***: mp 208–210°C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.46 (d, $J=7.32$ Hz, 2H), 8.33 (d, $J=6.84$ Hz, 1H), 8.02 (d, $J=8.30$ Hz, 1H), 7.42–7.24 (m, 9H), 6.29–6.21 (m, 1H), 6.05–5.98 (m, 1H), 5.59–5.54 (m, 1H), 4.56–4.53 (m, 1H), 4.26–4.09 (m, 4H), 3.01–2.77 (m, 2H), 1.52–1.50 (m, 3H), 1.25–1.10 (m, 3H), 0.86–0.83 (m, 6H); CIMS (m/z): 571 (M^+, M^++1, 37), 428 (55), 386 (100), 358 (45), 273 (67), 202 (42), FTIR (neat): 3278, 2926, 1638 cm^{-1}.
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8. **Procedure for intramolecular Heck reactions**: To a solution of **8** (0.07 g, 0.103 mmol) in acetonitrile (120 mL) was added palladium acetate (0.0014 g, 0.0062 mmol) and tri-(*o*-tolyl)phosphine (0.0028 g, 0.0093 mmol), followed by diisopropyl ethylamine (0.027 mL, 0.155 mmol). The reaction mixture was refluxed for 36 h and then diluted with dichloromethane. It was filtered through Celite and the filtrate was concentrated in vacuo. The residue was then dissolved in dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated; column chromatography (100–200 mesh silica gel, 2:3 hexane/ethyl acetate) afforded the desired product **2** as a thick colorless oil (0.027 g, 45%).
Spectral data for ***1***: mp 290–292°C; ^{1}H NMR (CD_3OD, 200 MHz): δ 7.9 (m, 1H), 7.54–7.12 (m, 10H), 6.92 (d, $J=12.2$ Hz, 1H), 5.94 (d, $J=12.62$ Hz, 1H), 4.49–4.21 (m, 5H), 3.01–2.95 (m, 2H), 1.80–1.64 (m, 3H), 1.22 (d, $J=8.79$ Hz, 3H), 1.09–0.87 (m, 6H); FTIR (neat): 3380, 2956, 1655 cm^{-1}; CIMS (m/z): 491 (M^++1, 100), 434 (50), 334 (17), 291 (21), 181 (45).
Spectral data for ***2***: ^{1}H NMR (CD_3OD, 400 MHz): δ 8.62 (d, $J=10$ Hz, 1H), 8.05 (m, 1H), 7.42–7.11 (m, 15H), 7.04 (d, $J=7.6$ Hz, 1H), 6.72 (d, $J=6.4$ Hz, 1H), 6.64 (d, $J=16.4$ Hz, 1H), 5.51–5.49 (m, 1H), 5.40–5.27 (m, 1H), 4.99 (q, $J=7.2$ Hz, 1H), 4.85 (q, $J=6$ Hz, 1H), 4.71–4.67 (m, 1H), 4.42 (d, $J=6.4$ Hz, 2H), 3.16 (dd, $J=7.2$, 8.4 Hz, 2H), 2.71–2.67 (m, 2H), 1.58 (m, 1H), 0.89 (d, $J=6.4$ Hz, 3H), 0.86 (d, $J=6.4$ Hz, 3H); CIMS (m/z): 567 (M+1, 65), 526 (25), 494 (100), 462 (27), 349 (38), 278 (13), 202 (17), 176 (13), 131 (12), 91 (11); $[\alpha]_D=+98$ (c 0.25, MeOH).