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Synthesis of 1,2-Disubstituted Pyrroles: A Cis Peptide Bond Surrogate

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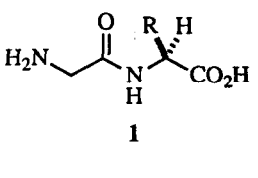
Key Words: Cis peptide bond surrogate; Dipeptide; Glycine; 1,2-Disubstituted pyrroles

Abstract: 1,2-Disubstitutd pyrroles have been synthesized as surrogates of a Gly-X dipeptide cis peptide bond

Conformationally restricted peptide and amino acid analogues, for example *N*-methyl amino acids[1], αα-disubstituted amino acids[2], β– and γ-bend mimics[3], dipeptide lactams[4] and others[5] have been used extensively to study the biologically important conformational preferences of bio-active peptides. This work has important applications in the probing of receptor specificity and in developing bioactive peptides with enhanced stability, selectivity and potency[6]. Surrogates of the *trans* **1** and *cis* **2** forms of a peptide bond have attracted considerable interest in this context. The *cis* peptide geometry, although usually disfavoured, is particularly important in polypeptide folding[7] and has been observed in both cyclic[8] and linear[9] peptides. A *trans* olefinic moiety[10] has been successfully employed to mimic the *trans* configuration **1** but the analogous *cis* olefinic group is an unsatisfactory mimic of **2** due to the ease of *cis/trans* olefin isomerism. The 1,5-tetrazole ring ψ[CN_4][11,12] and simple racemic o-aminomethylphenylacetic acid derivatives[13] have recently been developed as alternative amide bond surrogates for a *cis* peptide bond. The tetrazole formation gave some problems with racemization and the success of the preparation was found to be dependent upon the amino protecting group employed and also upon the dipeptide amino acid sequence.



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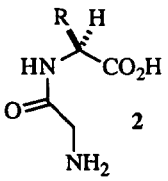

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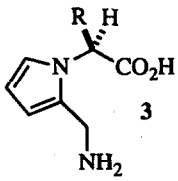

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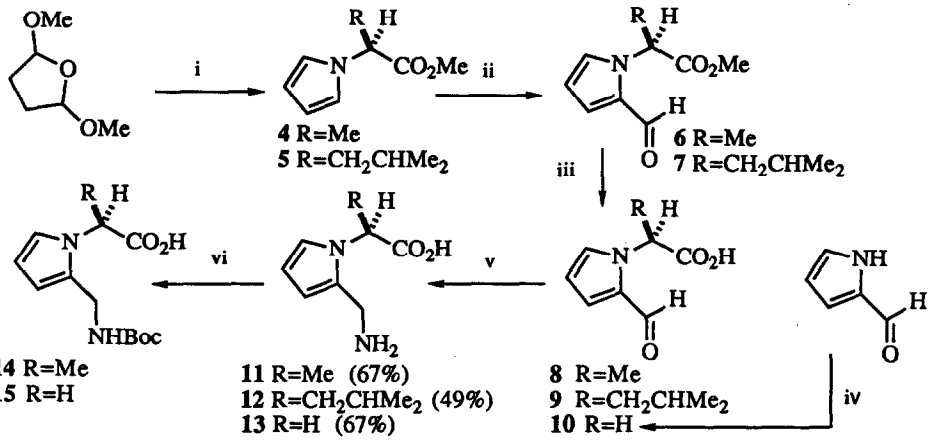
Here, we report a simple preparation of unprotected Gly-X dipeptide surrogates **3** which contain a 1,2-pyrrole ψ[C_4N] moiety designed to mimic a *cis* amide bond. *N*-protection is conveniently introduced at the completion of the synthesis.

1,4-Dimethoxytetrahydrofuran was treated[14] with the methyl ester hydrochloride of either L-alanine or L-leucine to give **4** and **5**, respectively. Formylation and ester hydrolysis[15] then gave **8** and **9**. The glycine analogue **10** was more conveniently prepared[16] by alkylation of pyrrole-2-carboxaldehyde with bromoacetic acid. The desired Gly-ψ[C_4N]-Gly *cis* peptide surrogate **13** crystallized[17] directly from an ammonium acetate buffered $NaCNBH_3$ reductive ammination[18] of **10** in MeOH. The Gly-ψ[C_4N]-Ala and Gly-ψ[C_4N]-Leu analogues **11** and **12**, respectively, were isolated from a similar reductive amination by first evaporating the MeOH, partitioning between water and ethyl acetate and freeze drying. An attempted reductive ammination of the ethyl ester of **10** gave a very low yield of the corresponding amine and consequently the free acids **8-10** were used. Boc protection is conveniently introduced using BOC-ON® according to well established conditions[19]. The *cis* dipeptide surrogates are readily extended in the C-direction by coupling with a C-protected amino acid using DCC and HOBt under standard conditions[20]. The ^1H NMR spectrum of Boc-Gly-ψ[C_4N]-Ala-Phe-OEt prepared from **14** gave no evidence of diastereomeric tripeptides.



Reagents and conditions: i. HCl-amino acid-OMe/$MeCO_2K/H_2O/MeCO_2H$, reflux 4h; ii. $CH(OMe)_3/TiCl_4/CH_2Cl_2$ -40° 1.5h; iii. $NaOH/H_2O$/MeOH, reflux 18h; iv. $BrCH_2CO_2H$/NaOH, RT 18h; v.$NaCNBH_3/MeCO_2NH_4$/MeOH (pH 7.25) RT, 18h; vi. (a) BOC-ON/acetone/H_2O/Et_3N, RT 18h. (b) 5 M HCl, pH 2.

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17. Preparation of **12**. $NaCNBH_3$ (0.8 equiv) was added to **9** (310mg) and ammonium acetate (8 equiv) in MeOH (7 mL). **12** was isolated by vacuum filtration as a hydroscopic solid after 18h stirring at RT. Data for **12**: mp 167-171°. ^1H NMR (300MHz, D_2O) δ 4.13 (2H, s); 4.49 (2H, s); 6.13 (1H, m); 6.33 (1H, m); 6.76 (1H, m). ^{13}C NMR (D_2O) δ 41.4, 51.6, 108.6, 113.3, 123.0, 126.7, 177.5. IR (KBr) 3191, 2361, 1576 cm^{-1}. Found C, 49.12; H, 6.98; N, 16.46. $C_7H_{10}NO_2(H_2O)$ requires C, 48.83; H, 7.02; N, 16.27%.
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