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A New Approach for Modification of Phenylalanine Peptides by Suzuki–Miyaura Coupling Reaction

Sambasivarao Kotha* and Kakali Lahiri†

Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai 400 076, India

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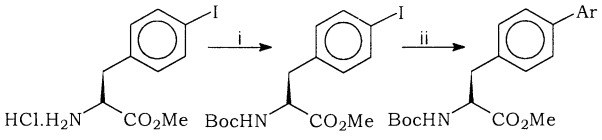
Abstract—For the first time, we have modified phenylalanine peptides by the Suzuki–Miyaura coupling reaction which may be useful in developing combinatorial libraries of peptidomimetics.

Peptides are natural messenger molecules of the human body and hence ideal lead compounds for initiation of drug discovery research. Examples of disorders for which peptide-based therapy exists include osteoporosis, diabetes, hypertension and diuresis. However, unfavourable pharmacological properties, such as non-selectivity, poor oral availablity and rapid proteolysis, limit severely the clinical usage of unmodified native peptides.[1] It is a general goal of peptide research to aim for structure modifications that may confer oral absorptivity, metabolic stability or function specificity, thus improving the pharmacological profile of a native peptide.[2] Molecular modifications are either undertaken rationally to alter the stucture or conformational features of the peptide pharmacophore, or combinatorially followed by screening to look for variant that will display desired modification in the activity profiles. A common theme of both peptidomimetics and combinatorial chemistry research is that stereochemical restraints are introduced into the native pharmacophore and, chemistries to introduce such restraints directly in the peptide architecture evoke interest in the rapidly developing field of combinatorial chemistry.[3]

In connection with our interest to prepare unusual α-amino acid derivatives and peptide modifications we have conceived a 'building block approach'[4,5] for the generation of large number of compounds starting from a common precursor. By using our 'building block approach' one will be in a position to synthesise a series of oligopeptides without having to repeat the whole sequence of peptide synthesis. Such a procedure might even provide multitude of peptides, which could not possibly be made from component amino acids because the individual amino acid may require special coupling methods and/or require special protecting groups.

As a part of research program,[6] we were interested in using the Suzuki–Miyaura coupling reaction[7]as a key step in the modification of the peptides. Aromatic AAAs like phenylalanine and tyrosine are important structural elements in several peptide pharmacophores. To test this idea initially, the Suzuki coupling reaction on simple AAA derivative was attempted. In this regard, the known compound **2**,[8] obtained from commercially available 4-iodo-L-phenylalanine was reacted with furanboronic acid in presence of tetrakis(triphenylphosphine)palladium(0) catalyst to give modified AAA **3** in 85% yield. Along similar lines, various arylboronic acid derivatives were reacted with **2** to give the corresponding coupling products **3**–**8** and the results are shown in Scheme 1. The structure of the coupling products were confirmed by 300 MHz ^{1}H NMR spectral data.



Scheme 1. Reagents and conditions (i) $(Boc)_2O$, $CHCl_3$, Et_3N (ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3–H_2O, THF/toluene (1:1).

*Corresponding author. Tel.: +91-22-576-7160; fax: +91-22-572-3480; e-mail: srk@chem.iitb.ac.in
†Née Chakraborty.

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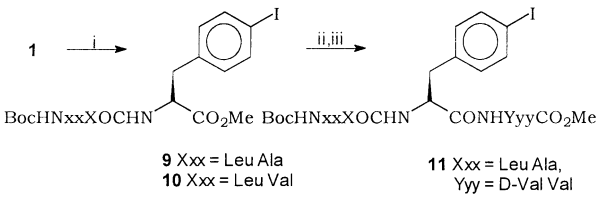


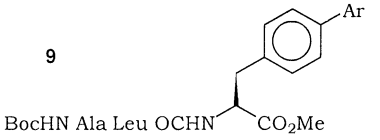
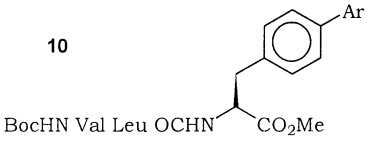
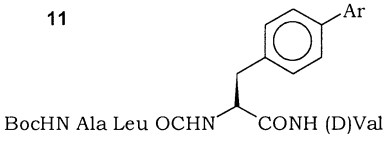
Scheme 2. Reagents and Conditions. (i) $BocHNXxxCO_2H$, HOBt, EDC1, Dry THF, Et_3N; (ii) MeOH, NaOH; (iii) $BocNHYyyCO_2Me$, CF_3CO_2H, HOBt, EDC1, Dry THF, NMM.

Having established the Suzuki–Miyaura coupling reaction with compound **2**, attention was turned towards the modification of phenylalanine peptides. In this regard, the tripeptides **9** and **10** were prepared by the condensation of the ester protected amino acid building block **1** with various *tert*-butoxycarbonyl (Boc)-protected amino acid derivatives by standard DCC mediated peptide coupling strategy.[8] However, in each case, the tripeptide was found to be contaminated with the byproduct, dicyclohexyl urea (DCU). To avoid this problem, water-soluble DCC, 1-[3-(dimethylamino)propyl]3-ethylcarbodiimide hydrochloride (EDCl) was used for the coupling reaction. The peptides were purified by silica gel chromatography. The purity of the tripeptides was confirmed by TLC and high field (300 MHz) ^{1}H NMR spectral data. Suzuki–Miyaura coupling on these tripeptides was performed using the conditions developed in the case of phenylalanine AAA derivatives and the yields of the reactions were found to be good. Similarly, pentapeptide **11** was prepared from the tripeptide **9** using the same coupling protocol. The purity of the compounds was judged by TLC and 300 MHz ^{1}H NMR spectral data. The 300 MHz ^{1}H NMR spectrum of the peptide **11** in $CDCl_3$ showed three peaks instead of five amide peaks as expected. However, when the spectrum was recorded in DMSO-d_6, all the amide protons were accounted. Temperature dependence of NH shift experiment was carried on the pentapeptide **11** in DMSO-d_6.[9] It is noteworthy to mention that one of the amide proton at $\delta = 8$ ppm (at rooms temperature) was having $[\Delta\delta/T]$ value 2×10^{-3} ppm/°C. This indicates the amide proton is solvent shielded which may be due to intramolecular H-bonding with C=O moiety present in the peptide residue.

Then, attention was directed towards the modification of the pentapeptide **11**. In this regard, compound **11** was reacted with furan, thiophene and phenylboronic acids successively to generate various modified analogues and the results are summarized in Table 1. A typical experimental procedure for the Suzuki–Miyaura coupling reaction involves treatment of the iodo compound (1 equiv) with boronic acid (2 equiv) at 80 °C in presence of tetrakis(triphenylphosphine)palladium(0) (5 mol%) catalyst and aqueous sodium carbonate (2 equiv) in THF/toluene solvent. At the conclusion of the reaction (TLC), the two layers were separated and the aqueous layer was extracted with dichloromethane. The product was purified on a silica gel column by eluting with pet ether/ethyl acetate (Scheme 2).

In conclusion, for the first time we have demonstrated an exceptionally simple and versatile method for the modification of unusual phenylalanine peptides using Suzuki–Miyaura coupling reaction as a key step. This strategy which gave a good overall yield may be useful to prepare various biologically active peptides in a short period of time. Moreover, the strategy developed here may find useful application in developing combinatorial synthesis of peptidomimetics and therefore our results may find useful applications in bioorganic and medicinal chemistry.

Table 1. List of various modified phenylalanine peptide derivatives prepared by the Suzuki–Miyaura coupling reaction

Starting peptide	Coupling product	Ar (Yield%)
9		**12** Furyl (74) **13** Thienyl (86) **14** Phenyl (87)
10		**15** Furyl (74) **16** Thienyl (78) **17** Phenyl (82)
11		**18** Furyl (60) **19** Thienyl (69) **20** Phenyl (64)

Selected data for the compounds 3–20

3. $[\alpha]_D^{26}$57.29 (*c* 1, $CHCl_3$).[7e]

4. $[\alpha]_D^{26}-28.57$ (*c* 0.7, $CHCl_3$).

5. $[\alpha]_D^{26}$52.92 (*c* 1, $CHCl_3$).[7e]

6. $[\alpha]_D^{26}$57.99 (*c* 1, $CHCl_3$).[7e]

7. $[\alpha]_D^{26}$32.99 (*c* 1, $CHCl_3$).

8. $[\alpha]_D^{26}$ 24.44 (*c* 0.9, $CHCl_3$).

9. ^{1}H NMR 300 MHz $CDCl_3$. δ 0.87–0.92 (m, 6H), 1.32 (d, $J = 6.9$ Hz, 3H), 1.44 (s, 9H), 1.50–1.64 (m, 3H), 3.00 (dd, $J = 5.9$, 13.9 Hz, 1H), 3.11 (dd, $J = 5.9$, 13.9 Hz, 1H), 3.72 (s, 3H), 4.07–4.13 (m, 1H), 4.33–4.40 (m, 1H), 4.76–4.83 (m, 1H), 4.90 (bs, 1H), 6.61 (bs, 2H), 6.86 (d, $J = 8.1$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H); $[\alpha]_D^{26}-5.55$ (*c* 0.9, $CHCl_3$); mp 164 °C.

10. ^{1}H NMR 300 MHz $CDCl_3$. δ 0.87–0.92 (m, 9H), 0.97 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.49–1.65 (m, 3H), 2.11–2.21 (m, 1H), 3.00 (dd, $J = 6.6$, 13.9 Hz, 1H), 3.10 (dd, $J = 5.5$, 13.9 Hz, 1H), 3.71 (s, 3H), 3.87 (dd, $J = 5.9$, 8.1 Hz, 1H), 4.38–4.45 (m, 1H), 4.78 (dd, $J = 6.4$ Hz,

13.7, 1H), 4.97 (bs, 1H), 6.31 (bs, 1H), 6.67 (bs, 1H), 6.88 (d, $J=8.4$ Hz, 2H), 7.62 (d, $J=8.4$ Hz, 2H); $[\alpha]_D^{26}$22.99 ($c=1$, $CHCl_3$); mp. 153–154 °C.

11. ^{1}H NMR 300 MHz DMSO-d_6. δ 0.73–0.88 (m, 18H), 1.12 (d, $J=7.3$ Hz, 3H), 1.36 (s, 9H), 1.46–1.51 (m, 3H), 1.91–2.07 (m, 2H), 2.69–2.84 (m, 1H), 2.88–2.94 (m, 1H), 3.63 (s, 3H), 3.88–3.94 (m, 1H), 4.16–4.24 (m, 2H), 4.31–4.36 (m, 1H), 4.63–4.70 (m, 1H), 6.90 (d, $J=12.0$ Hz, 1H), 7.05 (d, $J=8.1$ Hz, 2H), 7.57 (d, $J=8.1$ Hz, 2H), 7.68 (d, $J=8.4$ Hz, 1H), 7.96–8.03 (m, 2H), 8.24 (d, $J=8.1$ Hz, 1H); $[\alpha]_D^{26}-25.71$ (*c* 0.7, $CHCl_3$); mp 245 °C.

12. ^{1}H NMR 300 MHz $CDCl_3$. δ 0.87–0.91 (m, 6H), 1.29 (d, $J=7.0$ Hz, 3H), 1.43 (s, 9H), 1.50–1.65 (m, 3H), 3.07 (dd, $J=6.3$, 13.9 Hz, 1H), 3.15 (dd, $J=6.0$, 13.7 Hz, 1H), 3.72 (s, 3H), 4.07–4.11 (m, 1H), 4.35–4.40 (m, 1H), 4.79–4.86 (m, 1H), 4.89 (bs, 1H), 6.44–6.46 (m, 1H), 6.55 (bs, 2H), 6.62 (d, $J=3.3$ Hz, 1H), 7.12 (d, $J=8.0$ Hz, 2H), 7.44 (s, 1H), 7.59 (d, $J=8.0$ Hz, 2H); $[\alpha]_D^{26}-23.33$ (*c* 0.6, $CHCl_3$); mp. 148–149 °C.

13. ^{1}H NMR 300 MHz $CDCl_3$. δ 0.82–0.91 (m, 6H), 1.29 (d, $J=7.0$ Hz, 3H), 1.43 (s, 9H), 1.48–1.69 (m, 3H), 3.08 (dd, $J=6.1$, 13.8 Hz, 1H), 3.16 (dd, $J=5.9$, 13.7 Hz, 1H), 3.72 (s, 3H), 4.12 (q, $J=7.1$ Hz, 1H), 4.37–4.44 (m, 1H), 4.84 (dd, $J=6.0$, 13.7 Hz, 1H), 4.96 (d, $J=7.0$, 1H), 6.62 (bs, 2H), 7.07 (dd, $J=3.6$ Hz, 5.0 Hz, 1H), 7.11 (d, $J=8.2$ Hz, 2H), 7.25–7.29 (m, 2H), 7.53 (d, $J=8.1$ Hz, 2H); $[\alpha]_D^{26}$5.99 (*c* 1, $CHCl_3$); mp. 163–164 °C.

14. ^{1}H NMR 300 MHz $CDCl_3$. δ 0.89 (t, $J=6.2$ Hz, 6H), 1.29 (d, $J=7.0$ Hz, 3H), 1.43 (s, 9H), 1.49–1.70 (m, 3H), 3.11 (dd, $J=6.0$, 13.9 Hz, 1H), 3.20 (dd, $J=6.0$, 14.0 Hz, 1H), 3.74 (s, 3H), 4.08–4.13 (m, 1H), 4.38–4.45 (m, 1H), 4.86 (dd, $J=6.0$, 13.6 Hz, 1H), 4.95 (d, $J=7.1$ Hz, 1H), 6.61 (bs, 2H), 7.16–7.59 (m, 9H); $[\alpha]_D^{26}$11.99 (*c* 1, $CHCl_3$); mp. 155–157 °C.

15. ^{1}H NMR 300 MHz $CDCl_3$. δ 0.84–0.90 (m, 9H), 0.94 (d, $J=6.6$ Hz, 3H), 1.44 (s, 9H), 1.49–1.67 (m, 3H), 2.12–2.18 (m, 1H), 3.07 (dd, $J=6.9$, 13.8 Hz, 1H), 3.14 (dd, $J=5.7$, 13.8 Hz, 1H), 3.71 (s, 3H), 3.88 (dd, $J=5.8$, 8.1 Hz, 1H), 4.40–4.46 (m, 1H), 4.81 (dd, $J=6.0$ Hz, 13.7, 1H), 4.97 (bs, 1H), 6.32 (d, J = 7.7 Hz, 1H), 6.46 (dd, $J=1.8$, 3.3 Hz, 1H), 6.64 (d, $J=2.9$ Hz, 1H), 6.66 (bs, 1H), 7.14 (d, $J=8.1$ Hz, 2H), 7.45 (d, $J=1.5$ Hz, 1H), 7.60 (d, $J=8.4$ Hz, 2H); $[\alpha]_D^{26}$55.00 (*c* 0.8, $CHCl_3$); mp. 134–136 °C.

16. ^{1}H NMR 300 MHz $CDCl_3$. 0.84–0.91 (m, 9H), 0.94 (d, $J=6.6$ Hz, 3H), 1.43 (s, 9H), 1.50–1.69 (m, 3H), 2.12–2.19 (m, 1H), 3.07 (dd, $J=6.6$, 13.9 Hz, 1H), 3.15 (dd, $J=6.0$, 13.9 Hz, 1H), 3.71 (s, 3H), 3.89 (dd, $J=5.7$, 7.9 Hz, 1H), 4.41–4.45 (m, 1H), 4.82 (dd, $J=6.2$, 13.9 Hz, 1H), 4.99 (d, $J=6.6$ Hz, 1H), 6.36 (bs, 1H), 6.68 (bs, 1H), 7.07 (dd, $J=3.7$, 5.1 Hz, 1H), 7.14 (d, $J=8.1$ Hz, 2H), 7.27 (d, $J=3.3$ Hz, 1H), 7.30 (d, $J=3.7$ Hz, 1H), 7.54 (d, $J=8.1$ Hz, 2H); $[\alpha]_D^{26}-12.50$ (*c* 0.4, $CHCl_3$); mp. 113–115 °C.

17. ^{1}H NMR 300 MHz $CDCl_3$. δ 0.07–0.91 (m, 9H), 0.94 (d, $J=6.8$ Hz, 3H), 1.43 (s, 9H), 1.50–1.67 (m, 3H), 2.12–2.19 (m, 1H), 3.12 (dd, $J=6.2$, 13.9 Hz, 1H), 3.19 (dd, $J=5.9$, 13.9 Hz, 1H), 3.72 (s, 3H), 3.89 (dd, $J=5.9$, 7.9 Hz, 1H), 4.42–4.49 (m, 1H), 4.84 (dd, $J=6.1$, 13.6 Hz, 1H), 4.99 (d, $J=7.1$ Hz, 1H), 6.38 (d, $J=7.3$ Hz, 1H), 6.68 (bs, 1H), 7.20 (d, $J=8.1$ Hz, 2H), 7.32–7.36 (m, 1H), 7.41–7.50 (m, 2H), 7.54 (d, $J=8.2$ Hz, 2H), 7.57–7.60 (m, 2H); $[\alpha]_D^{26}$11.99 (*c* 0.5, $CHCl_3$); mp. 137–139 °C.

18. ^{1}H NMR 300 MHz DMSO-d_6. δ 0.72–0.88 (m, 18H), 1.09 (d, $J=7.0$ Hz, 3H), 1.35 (s, 9H), 1.23–1.51 (m, 3H), 1.89–2.07 (m, 2H), 2.72–2.84 (m, 1H), 2.95–3.01 (m, 1H), 3.63 (s, 3H), 3.91–3.96 (m, 1H), 4.17–4.26 (m, 2H), 4.33–4.38 (m, 1H), 4.64–4.69 (m, 1H), 6.56 (dd, $J=1.8$, 3.3 Hz, 1H), 6.86 (d, $J=3.3$ Hz, 1H), 6.91 (d, $J=6.6$ Hz, 1H), 7.28 (d, $J=8.4$ Hz, 2H), 7.56 (d, $J=8.4$ Hz, 2H), 7.67 (s, 1H), 7.70–7.71 (m, 1H), 8.00 (t, $J=6.6$ Hz, 2H), 8.25 (d, $J=8.1$ Hz, 1H); $[\alpha]_D^{26}-24.28$ (*c* 0.7, $CHCl_3$); mp. 241 °C.

19. ^{1}H NMR 300 MHz DMSO-d_6. δ 0.67–0.88 (m, 18H), 1.10 (d, $J=6.9$ Hz, 3H), 1.35 (s, 9H), 1.14–1.56 (m, 3H), 1.89–2.10 (m, 2H), 2.76–2.84 (m, 1H), 2.94–3.11 (m, 1H), 3.63 (s, 3H), 3.91–3.96 (m, 1H), 4.17–4.26 (m, 2H), 4.33–4.38 (m, 1H), 4.64–4.72 (m, 1H), 6.92 (d, $J=7.7$ Hz, 1H), 7.11 (dd, $J=3.7$, 4.8 Hz, 1H), 7.27 (d, $J=8.1$ Hz, 2H), 7.43 (d, $J=2.9$ Hz, 1H), 7.49–7.52 (m, 3H), 7.69 (d, $J=8.1$ Hz, 1H), 7.99–8.02 (m, 2H), 8.25 (d, $J=8.4$ Hz, 1H); $[\alpha]_D^{26}-57.50$ (*c* 0.4, $CHCl_3$); mp. 250–251 °C.

20. ^{1}H NMR 300 MHz DMSO-d_6. δ 0.67–0.88 (m, 18H), 1.10 (d, $J=7.3$ Hz, 3H), 1.35 (s, 9H), 1.14–1.55 (m, 3H), 1.89–2.07 (m, 2H), 2.81–2.89 (m, 1H), 2.96–3.08 (m, 1H), 3.63 (s, 3H), 3.92–3.96 (m, 1H), 4.19 (dd, $J=6.6$, 8.4 Hz, 1H), 4.26–4.37 (m, 2H), 4.66–4.73 (m, 1H), 6.93 (d, $J=7.7$ Hz, 1H), 7.31–7.62 (m, 9H) 7.69 (d, $J=8.1$ Hz, 1H), 7.98–8.04 (m, 2H), 8.23 (d, $J=8.4$ Hz, 1H); $[\alpha]_D^{26}-11.66$ (*c* 0.6, $CHCl_3$); mp 242 °C.

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