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Synthesis of bis-armed amino acid derivatives via the alkylation of ethyl isocyanoacetate and the Suzuki–Miyaura cross-coupling reaction

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Summary. Two synthetic routes to bis-armed-α-amino acid derivatives are described. The first route involves alkylation of dibromo derivatives with ethyl isocyanoacetate under phase-transfer catalysis (PTC) conditions. The second route uses a palladium-mediated Suzuki–Miyaura cross-coupling reaction between a DL-4-boronophenylalanine derivative and aromatic diiodo (or dibromo) compounds.

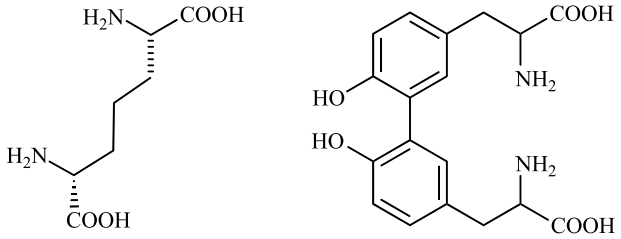
Keywords: Alkylation – Amino acids – DL-4-boronophenylalanine – Ethyl isocyanoacetate – Suzuki–Miyaura cross-coupling reaction

Introduction

Bis-armed-α-amino acids (BAAA) are key structural elements present in antibiotics that disrupt microbial cell wall synthesis (Nieto and Perkin, 1971a, b). For example, diaminopimelic acid (Cox et al., 2000; Williams and Yaun, 1994) (DAPA) **1** (Fig. 1) is an important cross-linking α-amino acid (AAA) in peptideglycan cell walls of gram-negative bacteria, possess antibiotic activity. Dityrosine **2** (Andersen, 1964) is a naturally occurring AAA, which helps to stabilize structural proteins in bacteria and plants. Various BAAA derivatives are also used as helix-turn-helix (HTH) motif of DNA-binding proteins (Rose et al., 1985). The phenyl ring acts as a hydrophobic core of the HTH motif. Mutual interaction of aromatic rings of these AAA residues in proteins and peptides was reported (Burley and Petskoo, 1985) and accordingly, the aromatic side-chains of these proteins and even of smaller peptides tend to align their aromatic rings in their domain with a relatively short distance between rings. The interaction between the aromatic rings seems to contribute to the stabilization of the tertiary structure of a protein. It was suggested that aromatic–aromatic interactions form an important class of non-covalent bonding in addition to H-bonding, electrostatic interactions and van-der Waal's interactions. Also, BAAA derivatives appear to be useful as ligands for the chelation of appropriate metals and the complexes thus formed can be used as chiral catalysts in asymmetric synthesis (Bělohradský et al., 2003; Kwik and Tay, 1989; Ionescu et al., 2003; Sandhu et al., 1989; Telfer et al., 2003).

In continuation of our interest in preparation of unusual AAA derivatives via ''building block approach'' (Kotha, 2003), we sought a general process applicable to a series of aromatic BAAA derivatives. In this regard, we thought that varying the degree of phenyl substitution is a useful exercise and also a synthetically challenging task. Despite the apparent simplicity of these BAAA, limited general methods are available in the literature as compared to DAPA analogues.

Burchalter et al. reported the preparation of BAAA derivatives via the alkylation of ethyl acetamidomalonate with xylylene dibromides (Burckhalter and Stephens, 1951). Recently, Frejd et al. have prepared unusual bis- and tris-armed AAA derivatives with good stereoselectivity via Heck coupling reaction followed by asymmetric hydrogenation using ''Rh'' catalyst (Cartström and Frejd, 1991; Ritzén et al., 1998a, b; Ritzén and Frejd, 1998). BAAA derivatives having a heterocyclic moiety have also been prepared by the same strategy (Basu et al., 1997; Basu and Frejd, 1996). In another report, Schöllkopf's ''bis-lactim ether'' was used as a chiral auxiliary to prepare aliphatic BAAA derivatives as well as bis-alanine derivatives containing a heterocyclic moiety (Kremminger and Undheim, 1997; Lange and Undheim, 1998; Hammer et al., 1997). Grubbs and co-workers (O'Leary et al.,



1 2

Fig. 1. Natural products with bis-armed amino acid structure

1998) reported a synthesis of aliphatic BAAA derivatives via a template promoted dimerisation of C-allylated glycine involving ring-closing metathesis (RCM) (Armstron, 1998; Grubbs, 2004; Kotha and Sreenivasachary, 2001) as a key step. Although various glycine equivalents are available for the preparation of AAA derivatives, a Schiff base derived from a glycine ester is an obvious choice. Lygo et al. used such a glycine equivalent to assemble various BAAAs using N-anthracenylmethyl dihydrocinchonidium bromide as a PTC (Lygo et al., 1999, 2001).

In view of the importance of BAAA derivatives, the development of a short and efficient synthetic route to these molecules is worthy of systematic investigation. Earlier, we demonstrated that ethyl isocyanoacetate **3** is a useful glycine equivalent for dialkylation with 2 equivalents of benzyl bromide to deliver dibenzyl glycine derivatives under PTC conditions (Kotha and Behera, 2004). Application of the same protocol to higher analogs can be readily envisioned. Here, we report a full account of two useful approaches for the synthesis of BAAA derivatives. The first approach involves alkylation of ethyl isocyanoacetate with dibenzyl bromides and the second route involves the Suzuki–Miyaura (SM) cross-coupling reaction (Kotha et al., 2002; Miyaura and Suzuki, 1995) of a DL-4-boronophenylalalnine derivative with diiodo (or dibromo) aromatic compounds.

Materials and methods

General remarks

Analytical TLC was performed on (10×5 cm) glass plates coated with silica gel G or GF 254 (containing 13% $CaSO_4$ as a binder). Visualization of the spots was achieved either by exposure to I_2 vapor or UV light. Flash chromatography was performed using silica gel (100–200 mesh) and usually eluted with EtOAc and petroleum ether (bp 60–80 °C) mixtures. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Varian VXR 300 or Varian VXR 400 spectrometers using TMS as internal standard and $CDCl_3$ or DMSO-d_6 as solvent. The coupling constants (J) are given in hertz (Hz). High Resolution mass spectral data were recorded on Q-TOF micromass machine. UV spectral data were obtained (in $CHCl_3$) on Shimadzu UV-2100 or UV-260 instruments. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT IR spectrometer. Solid samples were recorded as KBr wafers and liquid samples were recorded neat. For all the reactions anhydrous $MgSO_4$ or Na_2SO_4 was used as drying agent after workup. DL-4-Boronophenylalanine **8** was purchased from Aldrich Chemical Co., Milwaukee, WI, USA. 1,2-Dibromobenzene **15** and 1,3-dibromobenzene **17** were purchased from Lancaster Limited, UK. The diiodo compounds **9a**–**10a** (Merksushev et al., 1980) and **11a** (Unore and Reinhardt, 1987; Zuhar et al., 1995) were prepared according to the literature procedures.

*Preparation of 3-[4-(2-Ethoxycarbonyl-2-isocyano-ethyl)-phenyl]-2-isocyanopropionic acid ethyl ester (**4c**)*

To a solution of α,α'-dibromo-*p*-xylelene **4b** (300 mg, 1.13 mmol), ethyl isocyanoacetate **3** (514 mg, 4.5 mmol) tetrabutylammonium hydrogensulphate (TBAHS) (250 mg, 0.73 mmol) in dry acetonitrile (25 ml) was added finely powdered potassium carbonate (1.88 g, 13.62 mmol). The resulting heterogeneous mixture was refluxed at 80 °C for 1.5 h. Then, the reaction mixture was cooled and filtered through a sintered glass crucible to remove the unwanted salts. The filtrate was concentrated under reduced pressure and extracted with diethyl ether ($25 \text{ ml} \times 3$), combined organic layers were washed with water (25 ml), brine (25 ml) and dried over $MgSO_4$. Removal of the solvent gave the crude product, which was purified by a silica gel column chromatography. Elution of the column with 3% ethyl acetate/petroleum ether mixture gave compound **4c** (60 mg, 16%) as a white solid.

Mp: 85–87 °C; $R_f = 0.45$ (petroleum ether – EtOAc, 3:1). UV ($CHCl_3$): λ_{max} (ε $M^{-1}\,cm^{-1}$) 261.5 (2.77×10^2) nm. IR (KBr) ν_{max}: 2152, 1743 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 6H), 3.13–3.28 (m, 4H), 4.22 (q, $J = 7.1$ Hz, 4H), 4.41–4.45 (m, 2H), 7.25 (s, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 14.0$, 38.5, 57.9, 62.8, 129.2, 134.0, 160.9, 166.0. Mass: m/z 328 (M^+).

*Preparation of 3-[4-(2-Ethoxycarbonyl-2-formylamnio-ethyl)-phenyl]-2-formyl-amino propionic acid ethyl ester (**4d**)*

To a stirred solution of isonitrile derivative **4c** (40 mg, 0.12 mmol) in diethyl ether (10 ml) and THF (5 ml) was added conc. HCl (2 drops) at 0 °C and stirred at RT for 1 h. The solvent was removed under reduced pressure and extracted with diethyl ether ($20 \text{ ml} \times 3$), combined organic layers were washed with water (25 ml), brine (25 ml) and dried over $MgSO_4$. Evaporation of the solvent gave the crude product which was purified by silica gel flash column chromatography. Elution of the column with 75% ethyl acetate/pet ether mixture gave N-formyl derivative **4d** (28 mg, 63%) as a white solid.

Mp: 129–130 °C. $R_f = 0.34$ (petroleum ethers – EtOAc, 4:1). UV ($CHCl_3$): λ_{max} (ε $M^{-1}\,cm^{-1}$) 263.5 (3.25×10^2) nm. IR (KBr) ν_{max}: 3322, 1731, 1658 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta = 1.27$ (t, $J = 7.1$ Hz, 6H), 3.09–3.19 (m, 4H), 4.20 (q, $J = 7.1$ Hz, 4H), 4.89–4.96 (m, 2H), 6.13 (d, $J = 7.1$ Hz, 2H), 7.05 (s, 4H), 8.14 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 14.2$, 51.8, 61.6, 129.6, 134.6, 160.3, 171.0. HRMS (EI) (for $C_{18}H_{24}N_2O_6$): Calcd: 364.16343; Found: 364.16386.

*Preparation of isocyano derivative (**5c**)*

A mixture of 4,4′-bis(dibromomethyl)biphenyl **5b** (100 mg, 0.29 mmol), ethyl isocyanoacetate **3** (133 mg, 1.18 mmol), finely grounded potassium carbonate (405 mg, 2.94 mmol) and TBAHS (50 mg) in dry acetonitrile (15 ml) was heated at 80 °C for 4 h (TLC monitoring). The reaction mixture was cooled to RT, filtered through sintered glass crucible and the solvent was evaporated. The residue was extracted with ethyl acetate ($20 \text{ ml} \times 3$), washed with water (50 ml), brine (50 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product was purified by a silica gel flash column chromatography. Elution of the column with ethyl

acetate-petroleum ether (4:96) mixture gave the alkylated product **5c** as a crystalline product (22 mg, 18%).

Mp: 134–136 °C; $R_f = 0.27$ (petroleum ether – EtOAc, 9:1). IR (neat): ν_{max} 2152, 1745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 6.9$ Hz, 6H), 3.2 (m, 4H), 4.2 (q, $J = 7.2$ Hz, 4H), 4.4 (m, 2H), 7.3 (d, $J = 7.8$ Hz, 4H), 7.5 (d, $J = 7.8$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.16$, 38.74, 57.97, 62.66, 96.28, 127.48, 129.89, 133.67, 140.22, 162.0, 165.81. EI Mass (QTOF): m/z = calcd. for ($C_{24}H_{24}N_2O_4$, M + 1): 405.1814; Found: 405.1800.

*Preparation of the amino ester (**5f**)*

A solution of the isocyano derivative **5c** (19 mg, 0.018 mmol) in absolute ethanol (3 ml) was added 2 drops of conc. HCl and the reaction mixture was stirred at RT for 3 h. Then, the solvent was evaporated under reduced pressure. The resulting white salt was dissolved in water (1 ml) and washed with diethyl ether (2 × 5 ml) to remove unwanted organic residues. The aqueous layer was basified with ammonia solution to ~pH 10 and then extracted with ethyl acetate (10 ml × 3). The combined organic extract was washed with water, brine and then dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave the amino ester as light yellow liquid (17.5 mg, 97%) and was directly used in next step without characterization. To a solution of amino ester **5e** (18 mg, 0.04 mmol) in chloroform (15 ml) was added Boc anhydride (22 mg, 0.117 mmol). The reaction mixture was refluxed at 65 °C for 72 h (TLC monitoring). The chloroform layer was evaporated and the residue was extracted with ethyl acetate, washed with water, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product was purified by a silica gel flash column chromatography. Elution of the column with ethyl acetate-petroleum ether (9:1) mixture gave N-Boc product **5f** as a white solid (16.0 mg, 59%).

Mp: 194–196 °C; $R_f = 0.66$ (petroleum ether – EtOAc, 7:3). IR (neat): ν_{max} 3385, 1752, 1715, 1376, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.2$ Hz, 6H), 1.42 (s, 18H), 3.12 (m, 4H), 4.10 (q, $J = 7.2$ Hz, 4H), 4.50 (d, $J = 7.9$ Hz, 2H), 7.19 (d, $J = 7.9$ Hz, 4H), 7.40 (d, 4H, $J = 7.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 28.5, 38.3, 54.6, 61.6, 80.1, 127.3, 130.0, 135.4, 139.6, 167.5, 172.1. EI Mass (QTOF): m/z = calcd. for ($C_{32}H_{44}N_2O_8$ + Na): 607.2995; Found: 607.2985.

*Preparation of DL-N-Boc-4-boronophenylalanine methyl ester (**8**)*

To a solution of DL-4-boronophenylalanine **6** (250 mg, 1.20 mmol) in methanol (10 ml), dry HCl gas (generated by dropwise addition of conc. H_2SO_4 to sodium chloride), was passed for about one and half hour. The resulting mixture was stirred at RT for 24 h. Then, the reaction mixture was concentrated under reduced pressure at 45–50 °C on rotary evaporator and kept under vacuum at 70 °C to give the methyl ester **7** (310 mg, 99%) and used without further purification for the next step.

IR (KBr) ν_{max}: 3200 (br), 2933, 2848, 1742, 1374 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 3.05$–3.202 (m, 2H), 3.66 (s, 3H), 4.28 (t, $J = 6.0$, 1H), 7.19 (d, $J = 7.2$ Hz, 2H), 7.75 (d, $J = 7.2$ Hz, 2H), 8.07 (s, 2H), 8.60 (s, 2H).

A solution of methyl ester **7** (300 mg, 1.16 mmol) in chloroform (20 ml) was taken in a three-neck RB flask. Then, triethyl amine (175 mg, 1.73 mmol) was added and the resulting mixture was stirred at RT for 10 minutes. Later, di-*tert*-butyl dicarbonate (345 mg, 1.50 mmol) was added. The reaction mixture was refluxed (65 °C) for 12 h and quenched with water and layers were separated. Aqueous layer was again extracted with $CHCl_3$ (20 ml × 3). Combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave compound **8** (343 mg, 92%).

$R_f = 0.35$ (petroleum ether – EtOAc, 7:3). IR (KBr) ν_{max}: 1742, 1682 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) (Kusturin et al., 2002): $\delta = 1.32$ (s, 9H), 2.81–2.99 (m, 2H), 3.60 (s, 3H), 4.15 (s, 1H), 7.18 (d, $J = 6.4$ Hz, 2H), 7.30 (d, $J = 7.2$ Hz, 1H), 7.69 (d, $J = 6.4$ Hz, 2H), 7.99 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 28.1$, 36.5, 51.8, 55.1, 78.3, 128.1, 134.1, 139.5, 155.4, 172.7.

General procedure for the SM cross-coupling reaction

In a three-neck RB flask attached with reflux condenser and nitrogen inlet-outlet, diiodo (or dibromo) compound (1 equi.), boronic acid **8** (4 equi.), Na_2CO_3 (4 equi.) in H_2O (1 ml) and THF/toluene (1:1, 4 ml) were charged. The reaction mixture was degassed for 20–30 mins. Palladium Catalyst $Pd(PPh_3)_4$ (10 mol%) was added to the above degassed mixture and resulting mixture was refluxed at 80–90 °C under N_2. At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched with water and extracted with dichloromethane (20 ml × 3). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product which was charged on a silica gel column. Elution of the column with ethyl acetate/petroleum ether mixture gave the desired product.

*Preparation of 4,4″-bis[2-(methoxycarbonyl)-2[(tert-butoxycarbonyl)-amino]ethyl]-p-terphenyl (**9b**)*

1,4-Diiodobenzene **9a** (40 mg, 0.12 mmol), boronic acid **8** (137 mg, 0.42 mmol), Na_2CO_3 (51.4 mg, 0.36 mmol) in H_2O (1 ml), $Pd(PPh_3)_4$ (14.0 mg, 10 mol%) in THF/toluene (1:1, 4 ml) were reacted as described in the general procedure. The crude product was purified by a silica gel column chromatography. Elution of the column with 10% ethyl acetate/petroleum ether mixture gave the scrambled product **12*** (16.0 mg, 12.5%). Further elution with 20% ethyl acetate/petroleum ether mixture gave the desired product **9b** (32 mg, 41%) as a white solid.

Mp: 186–190 °C; $R_f = 0.25$ (petroleum ether – EtOAc, 3:1). UV ($CHCl_3$) λ_{max} (ε M^{-1} cm^{-1}): 286 (29,902) nm. IR (KBr) ν_{max}: 3369, 1755, 1715, 1374, 1170 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.43$ (s, 18H), 3.07–3.21 (m, 4H), 3.75 (s, 6H), 4.63 (m, 2H), 5.03 (d, $J = 7.6$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 4H), 7.57 (d, $J = 8.0$ Hz, 4H), 7.65 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 28.4$, 38.1, 52.4, 54.5, 80.1, 127.2, 127.4, 129.9, 135.3, 139.4, 139.7, 155.2, 172.4. HRMS (EIMS): (m/z for $C_{36}H_{44}N_2O_8$) Calcd: 632.3097; Found: 632.3041.

*Preparation of 4,4‴-bis[2-(methoxycarbonyl)-2[(tert-butoxycarbonyl)-amino]ethyl]-p-quaterphenyl (**10b**)*

4,4″-Diiodobiphenyl **10a** (30 mg, 0.07 mmol), boronic acid derivative **8** (71.6 mg, 0.22 mmol), Na_2CO_3 (31 mg, 0.29 mmol) in H_2O (1 ml), $Pd(PPh_3)_4$ (8.5 mg, 10 mol%) and THF/toluene (1:1, 4 ml) were reacted as described in the general procedure. The crude product was purified by a silica gel column chromatography. Elution of the column with 10% ethyl acetate/petroleum ether mixture gave scrambled product **12** (24.0 mg, 30%). Continued elution with 20% ethyl acetate/petroleum ether mixture gave the desired product **10b** (24 mg, 40%) as a white solid.

Mp: 194–200 °C; $R_f = 0.14$ (petroleum ether – EtOAc, 3:1). IR (KBr) ν_{max}: 3375, 1749, 1714, 1176 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.43$ (s, 18H), 3.08–3.21 (m, 4H), 3.75 (s, 6H), 4.64 (m, 2H), 5.04 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 4H), 7.59 (d, $J = 8.0$ Hz, 4H), 7.66–7.73 (m, 8H). ^{13}C NMR (CDCl3, 100 MHz): $\delta = 28.4$, 38.1, 52.4, 54.5, 80.1, 127.2, 127.5, 129.9, 135.3, 139.4, 139.6, 139.8, 155.2, 172.5. UV ($CHCl_3$) λ_{max} (ε M^{-1} cm^{-1}): 302 nm (45,286). HRMS (m/z for $C_{42}H_{48}N_2O_8$): Calcd: 708.3410; Found: 708.3403.

* Yield of **12** was calculated using boronic acid derivative **8** as a limiting agent.

*Preparation of Bis-armed amino acid derivative **11b***

4,4‴-Diiodo-*p*-terphenyl **11a** (40 mg, 0.08 mmol), boronic acid derivative **8** (107 mg, 0.33 mmol), Na_2CO_3 (34.0 mg, 0.32 mmol) in H_2O (1 ml), $Pd(PPh_3)_4$ (9.6 mg, 10 mol%) and THF/toluene (1:1, 4 ml) were reacted as described in the general procedure. The crude product was purified by a silica gel column chromatography. Elution of column with 1% methanol/dichloromethane mixture gave the scrambled product **12** (18 mg, 30%) and desired product **11b** (23.5 mg, 36%) as a white solid.

Mp: >240 °C (dec.). IR (KBr) ν_{max}: 3370, 3035, 2925, 2843, 1752, 1687, 1180 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.43$ (s, 18H), 3.12–3.20 (m, 4H), 3.75 (s, 6H), 4.66 (m, 2H), 5.03 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 7.6$ Hz, 4H), 7.59 (d, $J = 8.0$ Hz, 4H), 7.67–7.75 (m, 12H).

*Preparation of 4,4′-Bis[2-(methoxycarbonyl)-2[(tert-butoxycarbonyl)-amino]ethyl]-biphenyl (**14**)*

4-Iodo phenylalanine derivative **13** (40 mg, 0.1 mmol), boronic acid derivative **8** (47.7 mg, 0.15 mmol), Na_2CO_3 (21 mg, 0.19 mmol) in H_2O (1 ml), $Pd(PPh_3)_4$ (11.4 mg, 10 mol%) and THF/toluene (1:1, 4 ml) were reacted as described in the general reaction procedure. The crude product was purified by a silica gel column chromatography. Elution of the column with 10% ethyl acetate/petroleum ether mixture gave scrambled product **12** (26.8 mg, 51%). Continued elution with 20% ethyl acetate/petroleum ether mixture gave the desired product **14** (31.0 mg, 56%) as solid.

Mp: 192–196 °C; $R_f = 0.33$ (petroleum ether – EtOAc, 4:1). IR (KBr) ν_{max}: 3375, 1749, 1715, 1176, 874, 810 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz): $\delta = 1.42$ (s, 18H), 3.03–3.19 (m, 4H), 3.74 (s, 6H), 4.55 (m, 2H), 5.38 (d, $J = 8.1$ Hz, 2H), 7.21 (d, $J = 7.8$ Hz, 4H), 7.50 (d, $J = 8.1$ Hz, 4H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz): $\delta = 28.0$, 37.5, 51.9, 54.2, 79.5, 126.7, 129.4, 135.0, 138.9, 154.9, 172.1. HRMS (m/z for $C_{30}H_{40}N_2O_8$): Calcd: 556.2784; Found: 556.2832.

*Preparation of 4,4″-bis[2-(methoxycarbonyl)-2[(tert-butoxycarbonyl)-amino]ethyl]-o-terphenyl (**16**)*

1,2-Dibromobenzene **15** (30 mg, 0.13 mmol), boronic acid **8** (164.0 mg, 0.51 mmol), Na_2CO_3 (54 mg, 0.51 mmol) in H_2O (1 ml), $Pd(PPh_3)_4$ (14.5 mg, 10 mol%) and THF/toluene (1:1, 4 ml) were reacted as described in the general reaction procedure. The crude product was purified by a silica gel column chromatography. Elution of column with 8% ethyl acetate/petroleum ether mixture gave the scramble product **12** (28 mg, 15.5%). Continued elution with 10% ethyl acetate/petroleum ether mixture gave the desired product **16** (32.4 mg, 40%) as a liquid and self-coupled product **14** (10 mg).

$R_f = 0.25$ (petroleum ether – EtOAc, 8.5:1.5). IR (Neat) ν_{max}: 3362, 1744, 1715, 1368, 1167, 1057, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.42$ (s, 18H), 2.96–3.10 (m, 4H), 3.67 (s, 6H), 4.56 (m, 2H), 5.01 (m, 2H), 6.95–7.04 (m, 8H), 7.40 (s, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta =$ 28.3, 38.0, 52.1, 54.3, 79.9, 127.5, 128.8, 130.0, 130.4, 134.2, 140.0, 155.1, 172.2. EI Mass (QTOF): m/z = calcd. for ($C_{36}H_{44}N_2O_8$ + Na): 655.2995; Found: 655.3049.

*Preparation of 4,4″-bis[2-(methoxycarbonyl)-2[(tert-butoxycarbonyl)-amino]ethyl]-m-terphenyl (**18**)*

1,3-Dibromobenzene **17** (30 mg, 0.13 mmol), boronic acid **8** (164.0 mg, 0.51 mmol), Na_2CO_3 (54 mg, 0.52 mmol) in H_2O (1 ml), $Pd(PPh_3)_4$ (14.5 mg, 10 mol%) and THF/toluene (1:1, 4 ml) were reacted as described in the general reaction procedure. The crude product was purified by a silica gel column chromatography. Elution of column with 8% ethyl acetate/petroleum ether mixture gave the scramble product **12** (33.5 mg, 19%). Further elution with 10% ethyl acetate/petroleum ether mixture gave the desired product **18** (26 mg, 32%) as a liquid.

$R_f = 0.31$ (petroleum ether – EtOAc, 4:1). IR (Neat) ν_{max}: 3387, 1744, 1715, 1368, 1168, 1067, 771 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.43$ (s, 18H), 3.08–3.21 (m, 4H), 3.75 (s, 6H), 4.62 (m, 2H), 5.02 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.8$ Hz, 4H), 7.51–7.58 (m, 7H), 7.76 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta = 28.3$, 38.1, 52.4, 54.4, 80.1, 126.1, 127.4, 129.6, 129.8, 135.3, 139.9, 141.2, 141.4, 155.2, 172.4. EI Mass (QTOF): m/z = calcd. for ($C_{36}H_{44}N_2O_8$ + Na): 655.2995; Found: 655.3103.

*Preparation of orthogonally protected biphenyl based BAAA derivative (**20**)*

4-Iodo phenylalanine derivative **19** (40.0 mg, 0.07 mmol), boronic acid derivative **8** (50.1 mg, 0.15 mmol), Na_2CO_3 (16.5 mg, 0.15 mmol) in H_2O (1 ml), $Pd(PPh_3)_4$ (9.0 mg, 10 mol%) and THF/toluene (1:1, 4 ml) were reacted as described in the general reaction procedure. The crude product was purified by a silica gel column chromatography. Elution of column with 12.5% ethyl acetate/petroleum ether mixture gave the desired product **20** (32.6 mg, 63%) as a liquid.

$R_f = 0.17$ (petroleum ether – EtOAc, 4:1). IR (KBr) ν_{max}: 3375, 1749, 1715, 1176, 874, 810 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): $\delta =$ 1.43 (s, 9H), 3.06–3.19 (m, 4H), 3.73 (s, 3H), 4.60–4.65 (m, 1H), 4.71–4.76 (m, 1H), 5.02 (d, $J = 7.6$ Hz, 1H), 5.07–5.20 (m, 1H), 5.27 (d, $J = 8.0$ Hz, 1H), 7.05 (d, $J = 7.6$ Hz, 2H), 7.18 (d, $J = 8.0$ Hz, 2H), 7.28–7.34 (m, 10H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 28.4$, 38.0, 38.2, 52.3, 52.4, 54.6, 55.0, 67.2, 67.5, 80.1, 127.3, 128.2, 128.3, 128.68, 128.73, 128.76, 129.8, 129.9, 134.8, 135.2, 135.3, 136.4, 139.5, 139.7, 155.3, 155.8, 171.5, 172.5. EI Mass (QTOF): m/z = calcd. for ($C_{39}H_{42}N_2O_8$ + Na): 689.2839; Found: 689.3704.

Results and discussion

In view of our past experience, we identified ethyl isocyanoacetate as a useful glycine equivalent suitable for dialkylation with various electrophiles under mild reaction conditions to deliver several unusual AAA derivatives (Kotha and Brahmachary, 1997a, b, 2001; Kotha et al., 2002; Kotha and Sreenivasachary, 1998). In this context, we found that ethyl isocyanoacetate was alkylated with *p*-xylylene dibromide **4b** ($n = 1$) under PTC conditions (Fig. 2) to deliver the BAAA derivative **4c** in 16% yield. Since the isocyano derivative **4c** was found to be unstable, it was hydrolyzed immediately to deliver the *N*-formyl derivative **4d** in 68% yield. Similarly, for the preparation of the higher analog, the dimethyl derivative **5a**, prepared via the SM cross-coupling reaction, was brominated under NBS conditions to generate the corresponding dibromide **5b** in 38% yield. Alkylation of ethyl isocyanoacetate with **5b** gave the bis-isonitrile derivative **5c** in 18% yield. Acid hydrolysis in presence of diethyl ether did not provide the expected *N*-formyl derivative **5d**. Therefore, **5c** was subjected to acid hydrolysis in ethanol to give the amino ester **5e** in 97% yield and the amino group was protected as a Boc-derivative under chloroform/$(Boc)_2O$/triethylemine (TEA) conditions to give the protected AAA derivative **5f** in 59% yield (Fig. 3).

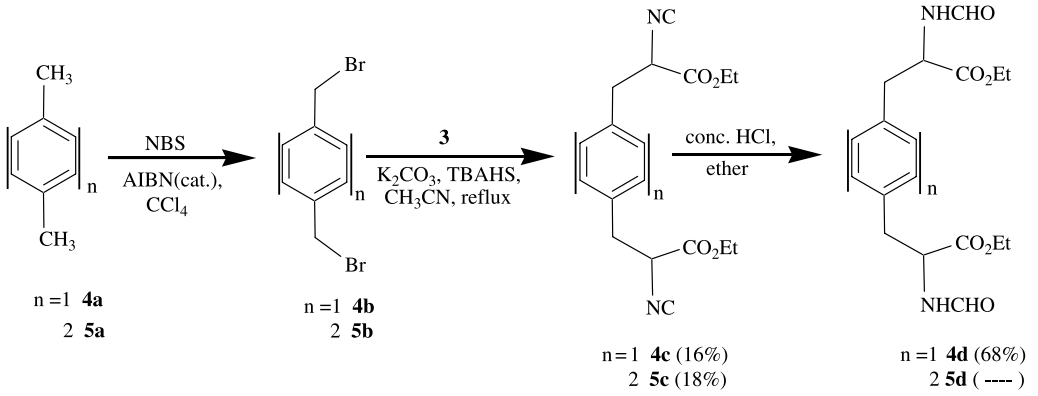


Fig. 2. Alkylation approach to BAAA derivatives

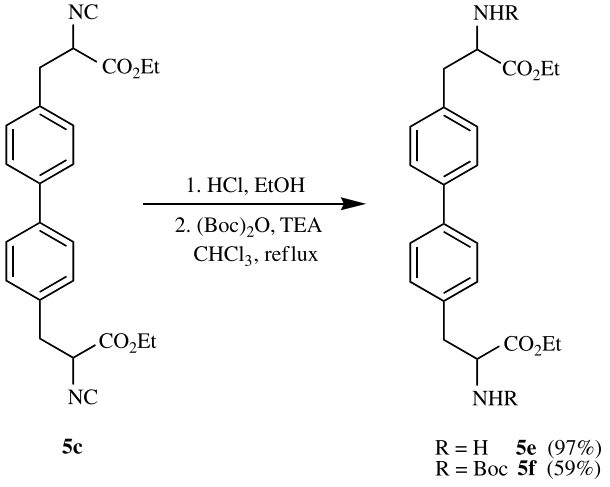


Fig. 3. N-Boc protection of **5c**

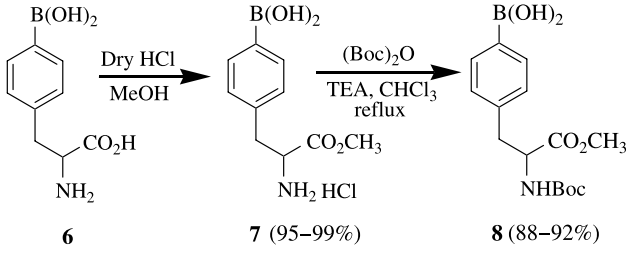


Fig. 4. Protection of DL-4-Borono phenylalanine

To prepare the higher analogs of BAAA derivatives, we envisioned the SM cross-coupling reaction as another useful option. Commercially available DL-4-boronophenylalanine **6** appears to be suitable coupling partner to prepare BAAA derivatives via the SM cross-coupling reaction. In this regard, we protected the carboxylic group present in **6** by esterification under acidic conditions to give the methyl ester **7** in 95–99% yield. The methyl ester **7** was next reacted with Boc-anhydride under TEA/$CHCl_3$/reflux conditions to give the N-Boc protected boronic acid derivative **8** in 88–92% yield (Fig. 4).

When the boronic acid **8** was subjected to SM cross-coupling under Pd(0) conditions [$Pd(PPh_3)_4$, aq. Na_2CO_3, THF/toluene, Fig. 5] with 1,4-diiodobenzene (Merksushev et al., 1980) **9a** ($m = 1$), the coupling product **9b** ($n = 3$) was obtained in 40% isolated yield along with the scrambled product **12** (Yield of **12** was calculated using boronic

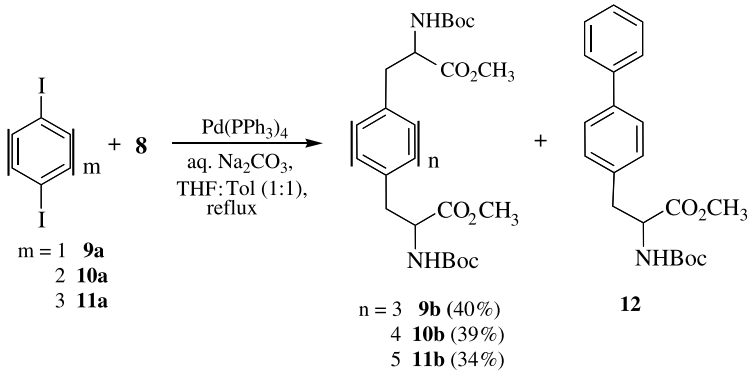


Fig. 5. SM cross-coupling approach to the linear BAAA derivatives

acid derivative **8** as a limiting agent). Generally, we observed the scrambled product **12** along with the required cross-coupling products. However, the self-coupling product **14** was observed when the aromatic dibromides- (or iodides-) were sterically hindered in nature. The cross-coupling product **9b** was characterized spectroscopically.

The ^{1}H NMR spectrum of **9b** showed a singlet at δ 1.41 corresponds to eighteen protons of the *tert*-butyl groups. In addition, the presence of two four-line pattern at δ 3.07–3.20 confirmed the presence of two benzylic ($-CH_2$) protons. A singlet at δ 3.75 corresponding to six protons of the two methyl ester groups, a multiplet at δ 4.63 of two protons (−CH group) and doublet at δ 5.03 (−NH proton) confirmed the methyl ester, methine group and amide group, respectively, and two doublets at δ 7.21, 7.57 corresponds to four protons and a singlet at δ 7.65 corresponds to two protons gave support to the *p*-terphenyl moiety. 13-Line ^{13}C NMR confirmed the symmetry present in the molecule **9b** and mass spectral data m/e [632.3041 (calcd: 632.3097)] in HRMS confirmed the structural formation of **9b**. Similarly, when 4,4′-diiodobiphenyl **10a** (Merksushev et al., 1980) ($m = 2$) and 4,4″-diiodo-*p*-terphenyl **11a** (Unore and Reinhardt, 1987; Zuhar et al., 1995) ($m = 3$) were subjected to the SM cross-coupling reaction with the protected boronic acid **8**, the cross-coupling products **10b** ($n = 4$) and **11b** ($n = 5$) were isolated in 39 and 34% yields, respectively.

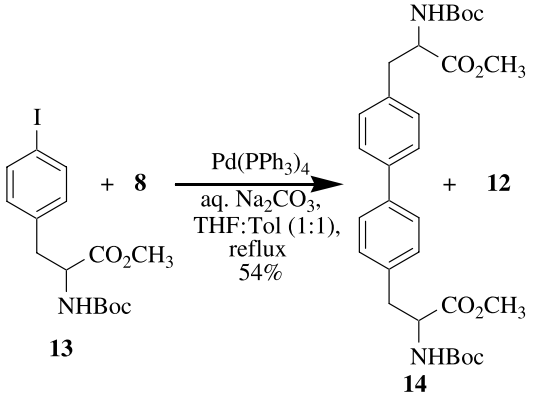


Fig. 6. SM cross-coupling approach to the linear BAAA derivatives

Next, L-4-Iodophenylalanine derivative **13** was coupled with the boronic acid **8**, to give the biphenyl derivative **14** in 54% yield (Fig. 6). Even though, optically active phenylalanine derivative **13** was used, the product obtained was racemic only, diastereomeric mixture was not observed from spectral data (^{1}H NMR and ^{13}C NMR). The reason for not observing the mixture of L, L or D, L diastereomers can be attributed to accidental degeneracy. Moreover, the two chiral centers are separated by biphenyl linker.

Having prepared several linear BAAA derivatives, next, the attention was turned to extend this methodology for the synthesis of angular BAAA derivatives. In this regard, 1,2-dibromobenzene **15** and 1,3-dibromobenzene **17** were coupled with the boronic acid derivative **8** to deliver the corresponding *o*-terphenyl BAAA derivative **16** and *m*-terphenyl BAAA derivative **18** in 40 and 34% yields, respectively (Figs. 7 and 8). During the coupling reaction of boronic acid derivative **8** with 1,2-dibromobenzene, scrambled product **12** and self-coupling product **14** were observed, however, in case of 1,3-dibromobenzene no self-coupling product **14** was observed, only scrambled product **12** was observed.

Orthogonally protected BAAA are useful in the synthesis of peptides because of the feasibility of selective deprotection. Frejd and co-workers had reported the synthesis of orthogonally protected *para*- and *meta*-phenylene bis-alanine and related biphenyl systems via combination of Heck coupling and asymmetric hydrogenations with Rhodium catalyst (Ritzén et al., 1998a).

So, we thought of synthesizing the BAAA with four different protecting groups using SM cross-coupling reaction. Towards this goal, we selected protected L-4-iodophenylalanine derivative **19** (Lei et al., 1994; Nakamura et al., 2000), coupled under SM reaction conditions with the boronic acid derivative **8**, the "orthogonally" protected biphenyl derivative **20** was isolated in 62% yield (Fig. 9). Compound **20** was found to be racemic based on the complementary spectral data (^{1}H NMR and ^{13}C NMR) and mixtures of L, L or D, L diastereomers were not observed can be attributed to the explanation given for the compound **13**.

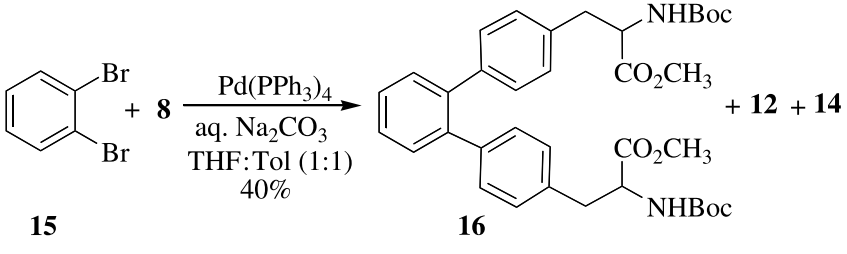


Fig. 7. Synthesis of angular BAAA derivative

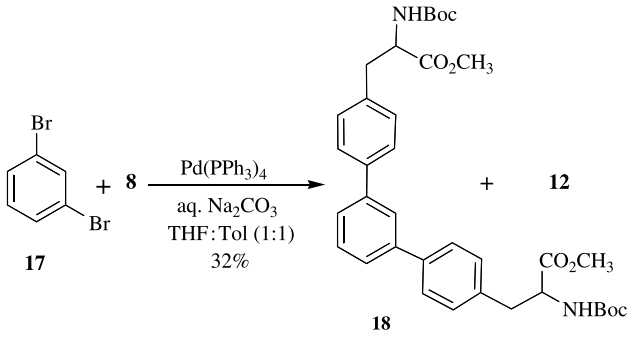


Fig. 8. Synthesis of angular BAAA derivative

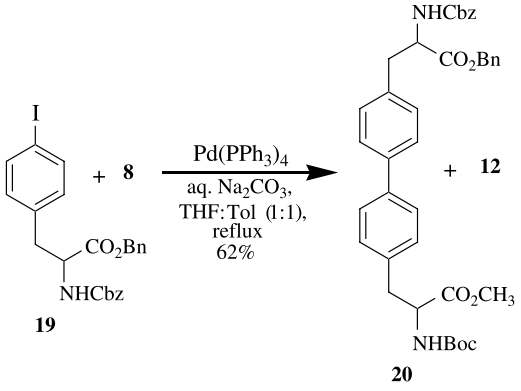


Fig. 9. Synthesis of "orthogonally" protected bis-armed amino acid derivative

Conclusion

We have prepared several unusual BAAA derivatives using two independent routes and these AAA derivatives may be incorporated in biologically active peptides or proteins to generate useful peptidomimetics. The SM cross-coupling reaction has been used for the synthesis of BAAA derivatives with variable numbers of benzene rings in linear as well as angular fashion. Also, ethyl isocyanoacetate has been used as a glycine equivalent to deliver the BAAA derivatives.

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