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An Efficient and Epimerization Free Synthesis of C-Terminal Arylamides Derived from α-Amino Acids and Peptide Acids via T3P Activation

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Abstract A high yield and rapid synthesis of enantiomerically pure N^{α}-protected amino/peptide acid arylamides using *n*-propylphosphonic anhydride (T3P) in presence of *N*-methylmorpholine is described. The generality of the reaction has been studied for various N^{α}-protected amino acids with diverse range of aromatic amines and coumarin derivatives.

Keywords Arylamides · T3P · 7-Amino-3-methyl coumarin

Introduction

Carboxamides are the most prevalent organic functional groups, especially as components of natural products, pharmaceuticals and backbone of peptides (Pattabiraman and Bode 2011). Amino acid derived arylamides are a class of carboxamides, widely used in the synthesis of polymers, dendrimers, peptidomimetics, inhibitors and as cell signaling molecules (Vemparala et al. 2006; Yin et al. 2006; Vinogradov 2005; Meegalla et al. 2008; Kirkland et al. 2008; Hang et al. 2006). They are used as substrates in chromogenic, fluorogenic and amperogenic enzymatic assays. Not only C-terminal peptide AMC (7-amino-4-methyl coumarin) arylamides have been used in fluorogenic assays to determine the activity of enzymes in blood coagulation (Kembhavi et al. 1993; Stepanov et al. 1977; Talanian et al. 1997; Ulfohn et al. 1968) but also amino acid derived *p*-nitroanilides are often employed as chromogenic substrates to determine the activity of proteolytic enzymes (Svendsen et al. 1972).

The reported protocols for the synthesis of N^{α}-protected amino acid arylamide involve the reaction of N^{α}-protected amino acid with aryl amine, via coupling reagents such as *N,N′*-dicyclohexylcarbodiimide, phosphorous reagents etc. and mixed anhydride method. (Nedev et al. 1993; Pozdnev 1994; Zimmerman et al. 1976; Fujiwara and Tsuru 1978; Sharma and Castellino 1990; Okada et al. 1982; Rijkers et al. 1995; Kato et al. 1978; Monatalbetti and Flaque 2005). Due to weak nucleophilicity of arylamines, highly activated carboxylic acid is required for complete conversion into arylamides. Evidently, each of the known methods suffer from some drawbacks, in-terms of low yield, racemization, some of the coupling reagents are hazardous, expensive and consumed in stoichiometric amounts, thus leading to significant amount of wastes. Dunetz et al. developed an efficient protocol for amide bond formation using T3P and pyridine for about 12–24 h (Dunetz et al. 2011). Hu et al. developed a novel protocol for the preparation of amino/peptide acid arylamides by the ligation of selenocarboxylate with an azide (Wu and Hu 2007). However, the bottle neck in this protocol is the difficulty in preparation of selenocarboxylates. Peter et al. synthesized N^{α}-protected amino/peptide acid arylamides via enzymatic acylation (Nuijens et al. 2009). The general applicability of this protocol discourages due to longer reaction duration and elevated temperature. Thus, the development of simple, milder and alternative method for aryl amidation is still of interest.

In recent years, T3P has been found to be efficient coupling reagent for the synthesis of peptides in terms of atom economy, high yield and lack of epimerization

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(Basavaprabhu et al. 2013). T3P is highly reactive cyclic phosphonic acid anhydride and also a water scavenger. T3P offers several advantages over traditional reagents such as low price, less toxicity, a lower tendency to induce epimerization, excellent purity, broad functional group tolerance and easy work up procedure leading to high yields. It has been employed in several other reactions such as conversion of carboxylic acids to aldehydes, dehydration of amides to nitriles (Meudt et al. 2005) and formamides to isonitriles (Meudt et al. 2005). The heterocycles including oxadiazoles (Augustine et al. 2009), substituted pyrimidines (Crawforth and Paoletti 2009), indoles (Desroses et al. 2011) and β–lactams (Crichfield et al. 2000) have also been synthesized using T3P as a dehydrating agent. Recently we demonstrated efficient applications of T3P for a range of amino acid, peptide derivatives i.e. N^{α}-protected amino or peptide acid derived acid azides (Basavaprabhu et al. 2010), hydroxamic acids (Vasantha et al. 2010), thio acids (Madhu et al. 2012), alcohols (Nagendra et al. 2012) and Weinreb amides (Sharanabai et al. 2013). As part of our continuing endeavor on the application of T3P, we herein demonstrate an efficient and high yielding synthesis of N^{α}-protected amino/peptide acid arylamides with chiral homogenity.

Materials and Methods

All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich company. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AMX 400 MHz and 75 MHz instrument with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on high resolution mass spectra (HRMS) Q–T of micro mass spectrometer. All the reactions were monitored using TLCs with pre coated silica gel plates purchased from Merck. Column chromatography was performed with Merck silica gel (100–200 mesh) at normal atmospheric pressure.

Typical Procedure for the Preparation of *N*-Protected Amino/Peptide Acid Arylamides

To a solution of N^{α}-protected amino/peptide acid (1.0 mmol) in CH_3CN, NMM (1.2 mmol) and 50 % T3P in EtOAc (2.4 mmol) were added at 0 °C and the solution was stirred for about 10 min then aryl amine (1.0 mmol) was added to the reaction mixture. The reaction was monitored by TLC. After completion of the reaction (1–3 h), the solvent was evaporated and the crude was extracted into EtOAc (20 mL). The organic layer was washed with 10 % HCl (10 mL × 2), 5 % Na_2CO_3 (10 mL × 2), water, brine and dried over anhydrous Na_2SO_4, evaporated the solvent to obtain the aryl amide in good yields as well as purity (70–94 %).

Spectral Data

Fmoc-Ala-Anilide (**2a**)

White solid, m.p. 193 °C, yield 94 %. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (d, 3H, J = 7.6 Hz), 4.11–4.22 (m, 4H), 6.94 (d, 2H, J = 6.6 Hz), 7.25–7.79 (m, 13H), 9.93 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.7, 46.8, 52.3, 67.4, 121.8, 124.5, 127.4, 128.2, 128.7, 129.5, 139.3, 140.8, 143.5, 156.1, 171.7. HRMS: *m/z* $[M+Na]^+$ calcd for $C_{24}H_{22}N_2O_3$: 409.1528, Found: 409.1523.

Fmoc-Tyr-2-Chloroanilide (**2b**)

White solid, m.p. 155–156 °C, yield 81 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.10–3.18 (m, 2H, J = 6.6 Hz), 4.45 (t, 1H, J = 5.2 Hz), 4.61 (d, 2H, J = 6.2 Hz), 4.82–4.86 (m, 1H), 5.63 (br, 1H), 6.61 (s, 2H), 6.92 (s, 2H), 7.18–7.54 (m, 12H), 10.15 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 36.8, 48.1, 54.2, 67.6, 115.1, 122.2, 125.4, 126.3, 126.8, 127.5, 128.7, 128.9, 129.5, 130.6, 131.8, 138.5, 141.1, 142.5, 155.1, 156.8, 171.6. HRMS *m/z* $[M+Na]^+$ calcd for $C_{30}H_{25}ClN_2O_4$: 535.1401, Found 535.1404.

Fmoc-Thr-4-Methylanilide (**2c**)

White solid, m.p. 165–166 °C, yield 85 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.37 (d, 3H, J = 6.4 Hz), 2.43 (s, 3H), 3.91–3.97 (m, 1H), 4.35 (t, 1H, J = 4.8 Hz), 4.62–4.70 (m, 3H), 5.86 (br, 1H), 6.91–7.02 (m, 3H), 7.23–7.58 (m, 9H), 9.91 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.6, 19.1, 47.3, 58.4, 65.4, 68.3, 120.7, 123.4, 125.9, 126.4, 127.8, 128.2, 128.7, 129.7, 133.4, 137.3, 141.0, 143.3, 156.8, 171.5. HRMS *m/z* $[M+Na]^+$ calcd for $C_{26}H_{26}N_2O_4$: 453.1791, Found 453.1728.

Fmoc-Asp(Bu^t)-3-Methylanilide (**2d**)

White solid, m.p. 131–133 °C, yield 83 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (s, 9H), 2.38 (s, 3H), 2.87–2.95 (m, 2H), 4.24 (t, 1H, J = 6.8 Hz), 4.45 (d, 2H, J = 6.8 Hz), 4.65–4.71 (m, 1H), 6.12 (br, 1H), 6.87 (d, 1H, J = 7.6 Hz), 7.25–7.71 (m, 11H), 8.48 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.9, 27.5, 38.1, 48.8, 52.5, 66.9, 82.6, 116.8, 120.5, 121.1, 125.2, 125.8, 127.5, 128.3, 129.4, 137.8, 139.3, 140.8, 144.5, 156.8, 169.1, 171.8. HRMS *m/z* $[M+Na]^+$ calcd for $C_{30}H_{32}N_2O_5$: 523.2209, Found 523.2205.

Fmoc-Phg-3-Methylanilide (**2e**)

White solid, m.p. 214–217 °C, yield 88 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.31 (s, 3H), 4.22–4.29 (m, 3H),

5.35 (d, 1H, $J = 7.2$ Hz), 6.72 (d, 1H, $J = 6.6$ Hz), 7.15–8.23 (m, 17H), 10.21 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.8, 46.1, 67.2, 119.0, 120.7, 125.5, 126.3, 127.7, 128.3, 128.7, 129.2, 129.8, 138.1, 138.7, 156.2, 169.6. HRMS *m/z* $[M + H]^+$calcd for $C_{30}H_{26}N_2O_3$: 463.2022, Found 463.2025.

Fmoc-Aib-4-Methylanilide (**2f**)

White solid, m.p. 221–222 °C, yield 65 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.48 (d, 6H, $J = 6.4$ Hz), 2.41 (s, 3H), 4.37 (t, 1H, $J = 5.2$ Hz), 4.68 (d, 2H, $J = 7.2$ Hz), 6.97 (d, 2H, $J = 6.8$ Hz), 7.13 (br, 1H), 7.28–7.81 (m, 10 H), 9.31 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.8, 24.9, 46.5, 60.3, 66.9, 121.3, 126.4, 127.8, 128.4, 128.7, 129.5, 134.2, 136.1, 141.1, 143.5, 156.8, 174.2. HRMS *m/z* $[M+Na]^+$calcd for $C_{26}H_{26}N_2O_3$: 437.4860, Found 437.4852.

Fmoc-Pro-3-Methylanilide (**2g**)

White solid, m.p. 181 °C, yield 81 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82–1.87 (m, 2H), 2.03–2.08 (m, 2H), 3.21 (t, 2H, $J = 4.8$ Hz), 4.21 (t, 1H, $J = 5.4$ Hz), 4.43 (t, 1H, $J = 5.0$ Hz), 4.69 (d, 2H, $J = 7.4$ Hz), 6.98 (d, 1H, $J = 7.2$ Hz), 7.28–7.53 (m, 11H), 8.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.1, 29.3, 47.2, 48.7, 60.5, 67.9, 118.3, 120.1, 120.7, 124.3, 126.1, 127.5, 127.9, 128.5, 131.2, 134.5, 139.7, 140.8, 143.7, 156.5, 171.1. HRMS *m/z* $[M+Na]^+$ calcd for $C_{26}H_{23}ClN_2O_3$: 469.1295, Found 469.1286.

Fmoc-Ser-3-Methylanilide (**2h**)

White solid, m.p. 190–192 °C, yield 88 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.31 (s, 3H), 3.62–3.67 (d, 2H, $J = 6.0$ Hz), 4.23–4.32 (m, 4H), 6.79 (d, 1H, $J = 6.8$ Hz), 7.15–7.91 (m, 11H), 8.17 (s, 1H), 9.92 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.5, 46.3, 62.8, 116.3, 120.3, 121.5, 124.8, 125.3, 127.6, 128.2, 129.0, 138.1, 139.5, 141.4, 144.3, 144.7, 156.5, 171.8. HRMS *m/z* $[M+Na]^+$, calcd for $C_{25}H_{24}N_2O_4$: 439.1634, Found 439.1641.

Cbz-Phe-4-Methylanilide (**2i**)

White solid, m.p. 157–159 °C, yield 83 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.31 (s, 3H), 3.13 (d, 2H, $J = 6.2$ Hz), 4.90–4.96 (m, 1H), 5.28 (s, 2H), 7.02 (d, 2H, $J = 6.4$ Hz), 7.19–7.41 (m, 10 H), 7.57 (d, 2H, $J = 6.4$ Hz), 8.95 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 22.3, 37.1, 53.1, 66.3, 121.8, 126.2, 127.3, 127.8, 128.4, 128.8, 129.5, 129.7, 133.6, 135.1, 139.2, 141.2, 155.8, 172.3. HRMS *m/z* $[M+Na]^+$, calcd for $C_{24}H_{24}N_2O_3$: 411.4487, Found 411.4491.

Cbz-Ala-4-Methoxyanilide (**2j**)

White solid, m.p. 179–180 °C, yield 82 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.42 (d, 3H, $J = 6.8$ Hz), 3.78 (s, 3H), 4.71–4.75 (m, 1H), 5.21 (s, 2H), 6.84 (d, 2H, $J = 5.8$ Hz), 7.15–7.23 (m, 6H), 7.57 (d, 2H, $J = 5.8$ Hz), 9.34 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.5, 48.2, 56.1, 66.3, 114.6. 122.8, 127.5, 127.9, 129.1, 131.7, 140.4, 155.2, 156.5, 171.2. HRMS *m/z* $[M+Na]^+$, calcd for $C_{18}H_{20}N_2O_4$: 351.1321, Found 351.1327.

Cbz-Phe-3,4-Difluoroanilide (**2k**)

White solid, m.p. 160–163 °C, yield 71 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.84 (d, 2H, $J = 6.8$ Hz), 4.32 (t, 1H, $J = 5.2$ Hz), 5.25 (s, 2H), 6.83 (d, 1H, $J = 7.2$ Hz), 7.17–7.38 (m, 11H), 7.64–7.72 (m, 2H), 10.21 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 35.1, 56.7, 67.5, 111.2, 115.8, 117.8, 125.2, 126.1, 126.8, 127.3, 128.8, 129.7, 135.4, 137.8, 141.2, 146.4, 147.3, 156.7, 172.5. HRMS *m/z* $[M+Na]^+$ calcd for $C_{23}H_{20}F_2N_2O_3$: 433.1340, Found 433.1325.

Boc-Ala-3-Chloroanilide (**2l**)

White solid, m.p. 181–182 °C, yield 81 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.37 (s, 9H), 1.51 (d, 3H, J =), 4.91–4.95 (m, 1H), 5.87 (br, 1H), 6.95 (d, 1H, J =), 7.41–7.63 (m, 3H), 8.95 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.4, 27.8, 49.5, 78.1, 119.3, 121.8, 125.1, 130.8, 133.2, 138.1, 156.3, 171.8. HRMS *m/z* $[M+Na]^+$ calcd for $C_{14}H_{19}ClN_2O_3$: 321.7550, Found 321.7549.

Cbz-Phe-4-Cyanoanilide (**2m**)

White solid, m.p. 171–172 °C, yield 73 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.53 (d, 2H), 3.15 (t, 1H, $J = 4.4$ Hz), 4.93 (s, 2H), 7.12–7.53 (m, 12H), 7.83 (d, $J = 6.6$ Hz, 2H), 8.12 (br, 1H), 10.35 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 36.8, 57.1, 65.4, 110.7, 118.6, 120.9, 122.7, 126.5, 126.8, 127.4, 127.9, 128.3, 128.7, 129.1, 130.3, 136.8, 137.5, 139.4, 156.1, 171.0. HRMS *m/z* $[M+Na]^+$, calcd for $C_{24}H_{21}N_3O_3$: 422.1481, Found 422.1478.

Boc-Val-3-Bromoanilide (**2n**)

White solid, m.p. 153–154 °C, yield 90 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (d, 6H, $J = 7.2$ Hz), 1.43 (s, 9H), 2.69–2.78 (m, 1H), 4.12–4.18 (m, 1H), 7.18–7.41 (m, 4H), 7.92 (br, 1H), 9.82 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.3, 26.5, 31.7, 57.8, 79.1, 120.4, 121.5, 123.4, 127.6, 130.1, 139.3, 156.5, 172.1. HRMS *m/z* $[M+Na]^+$ calcd for $C_{16}H_{23}N_2O_3$: 393.0790, Found 393.0788.

Fmoc-Ala-*p*-Nitroanilide (**2o**)

White solid, m.p. 184–185 °C, yield 75 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.33 (d, 3H, J = 4.2 Hz), 4.10 (t, 1H, J = 6.0 Hz), 4.35 (d, 2H, J = 6.2 Hz), 4.67–4.71 (m, 1H), 5.18 (br, 1H), 7.21–8.05 (m, 12H), 10.72 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 16.7, 44.7, 48.4, 67.3, 120.4, 121.5, 125.2, 126.4, 127.3, 127.7, 140.1, 141.5, 143.3, 143.8, 155.7, 170.2. HRMS calcd for $C_{24}H_{21}N_3O_5$ *m/z* 454.1379 $[M+Na]^+$, Found 454.1354.

Fmoc-Val-*p*-Nitroanilide (**2p**)

White solid, m.p. 198–199 °C, yield 71 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.97 (d, 6H, J = 7.2 Hz), 2.42–2.48 (m, 1H), 4.20–4.27 (m, 2H), 4.54 (d, 2H, J = 6.8 Hz), 5.31 (br, 1H), 7.28–8.12 (m, 12H), 9.8 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 16.8, 30.5, 45.7, 58.5, 67.6, 121.2, 121.6, 125.5, 126.8, 127.4, 127.8, 140.0, 141.5, 143.3, 143.9, 155.0, 171.1. HRMS *m/z* $[M+Na]^+$ calcd for $C_{26}H_{25}N_3O_5$: 482.1692, Found 482.1680.

Fmoc-Gly-Phe-3-Methylanilide (**4a**)

White solid, m.p. 237–238 °C, yield 85 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.35 (s, 3H), 3.12–3.16 (m, 2H, J = 5.8 Hz), 3.78 (s, 2H), 4.35 (t, 1H, J = 5.4 Hz), 4.42–4.61 (m, 3H), 6.78 (d, 1H, J = 6.8 Hz), 7.21–7.63 (m, 18H), 9.21 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 25.8, 33.8, 40.7, 46.9, 52.8, 67.4, 118.4, 121.7, 123.4, 126.2, 126.8, 127.2, 127.8, 128.2, 128.9, 129.4, 137.9, 138.5, 139.8, 140.1, 143.2, 156.7, 169.7, 171.8. HRMS *m/z* $[M+Na]^+$ calcd for $C_{33}H_{31}N_3O_4$: 556.2212, Found 556.2215.

Fmoc-Val-Ala-4-Chloroanilide (**4b**)

White solid, m.p. 239–243 °C, yield 91 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (d, 6H, J = 7.2 Hz), 1.38 (d, 3H, J = 6.8 Hz), 2.51–2.59 (m, 1H), 4.43–4.5 (m, 2H), 4.52 (d, 2H, J = 6.8 Hz), 4.81–4.86 (m, 1H), 6.82 (br, 1H), 7.24–7.91 (m, 13H), 9.51 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 16.7, 18.1, 30.2, 45.8, 49.4, 57.1, 65.2, 123.7, 126.2, 127.4, 128.0, 128.5, 128.9, 129.4, 137.1, 139.2, 143.7, 156.2, 170.3, 172.7. HRMS *m/z* $[M+Na]^+$ calcd for $C_{29}H_{30}ClN_3O_4$: 542.1823, Found 542.1830.

Fmoc-Ala-Leu-4-Methoxyanilidine (**4c**)

White solid, m.p. 242 °C, yield 93 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.02 (d, 6H, J = 7.0 Hz), 1.35 (d, 3H, J = 6.4 Hz), 1.81–1.87 (m, 3H), 3.65 (s, 3H), 4.48–4.56 (m, 3H), 4.61 (d, 2H, J = 6.8 Hz), 6.75 (d, 2H, J = 7.0 Hz), 7.28–7.53 (m, 12H), 9.12 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.4, 20.3, 21.9, 41.2, 48.5, 50.3, 51.5, 56.1, 67.6, 115.6, 122.2, 126.0, 127.8, 128.6, 131.5, 140.2, 142.8, 156.5, 156.4, 170.5, 171.8. HRMS *m/z* $[M+Na]^+$ calcd for $C_{31}H_{35}N_3O_5$: 552.2474, Found 552.2478.

Cbz-Phe-Leu-2-Chloroanilide (**4d**)

White solid, m.p. 231–232 °C, yield 88 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (d, 6H, J = 7.2 Hz), 1.81–1.85 (m, 2H), 2.88 (d, 2H, J = 6.6 Hz), 4.37–4.46 (m, 3H), 5.27 (s, 2H), 5.81 (br, 1H), 6.97–7.24 (m, 14H), 7.45 (br, 1H), 9.52 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.8, 23.4, 35.8, 42.1, 51.4, 53.5, 15.8, 123.7, 125.2, 125.9, 126.4, 127.3, 127.8, 128.0, 128.3, 128.7, 129.3, 131.8, 134.6, 139.1, 141.4, 156.5, 170.8, 171.5. HRMS *m/z* $[M+Na]^+$ calcd for $C_{29}H_{32}ClN_3O_4$: 544.1979, Found 544.1969.

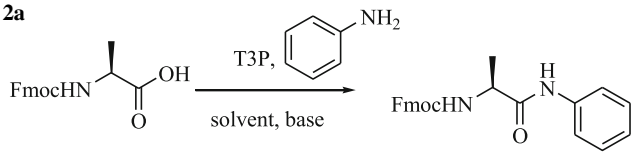
Boc-Ala-Ile-4-Methylanlide (**4e**)

White solid, m.p. 219–222 °C, yield 86 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.90 (t, 3H, J = 5.0 Hz), 1.07 (d, 3H, J = 6.8 Hz), 1.18–1.21 (m, 2H), 1.36 (s, 9H), 1.49 (d, 3H, J = 7.2 Hz), 2.31–2.37 (m, 1H), 2.51 (s, 3H), 4.48 (d, 1H, J = 6.2 Hz), 5.61 (br, 1H), 6.84 (br, 1H), 7.12 (d, 2H, J = 5.8 Hz), 7.64 (d, 2H, J = 5.6 Hz), 8.67 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.1, 15.2, 18.4, 23.5, 24.6, 28.1, 35.4, 49.7, 54.1, 78.5, 120.8, 129.1, 133.5, 135.1, 156.7, 170.1, 172.3. HRMS *m/z* $[M+Na]^+$ calcd for $C_{29}H_{32}ClN_3O_4$: 414.2369, Found 414.2365.

Boc-Gly-Val-4-Pyrrolylanilide (**4f**)

White solid, m.p. 229 °C, yield 82 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15 (d, 6H, J = 7.0 Hz), 1.37 (s, 9H), 2.31–2.37 (m, 1H), 3.78 (d, 2H, J = 6.2 Hz), 4.40 (d, 1H, J = 6.6 Hz), 5.57 (br, 1H), 6.18 (d, 2H, J = 5.8 Hz), 6.80 (d,

Table 1 Optimization of the reaction conditions for the synthesis of **2a**



2a

Entry	Base	Solvent	Yield (%)	Time (h)
1	Pyridine	EtOAc	65	18
2	Pyridine	THF	85	18
3	Pyridine	CH_3CN	90	15
4	DIPEA	CH_3CN	78	7
5	NMM	EtOAc	82	3
6	NMM	THF	85	2
7	NMM	CH_3CN	95	1

Table 2 List of *N*-protected amino acid arylamides **2**

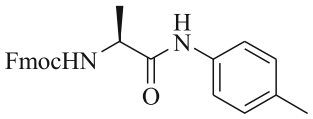
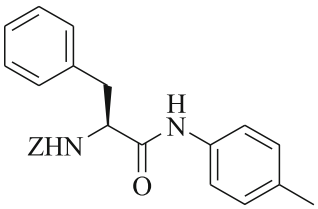
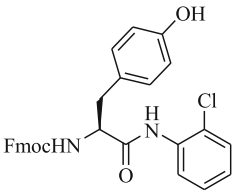
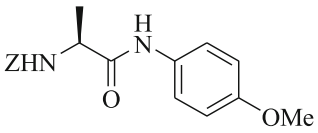
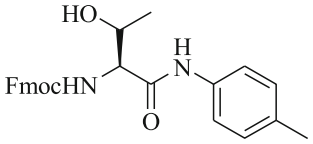
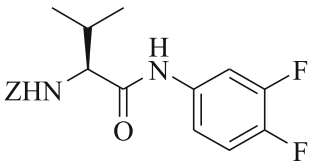
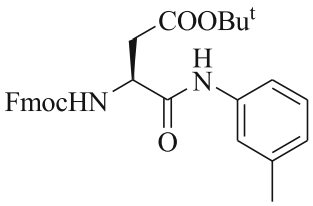
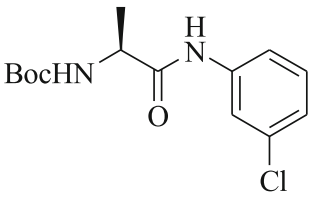
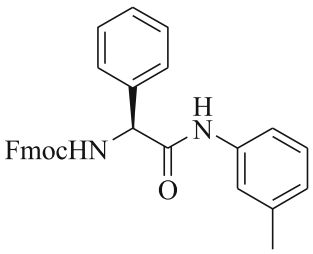
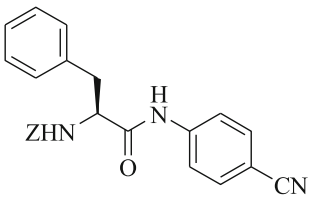
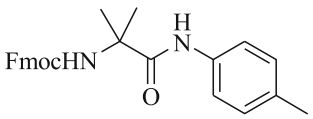
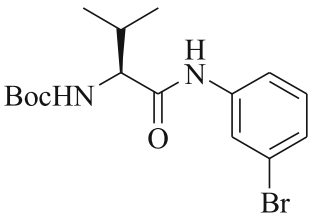
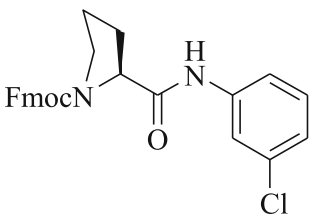
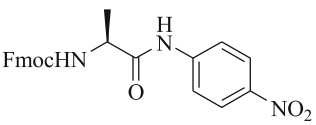
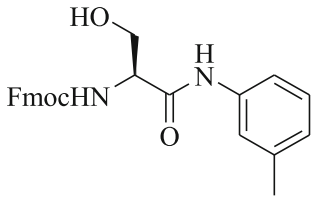
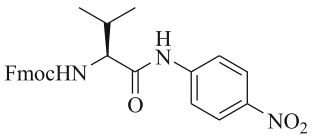
S.no	Arylamide 2	Yield (%)	Mp (°C)	S.no	Arylamide 2	Yield (%)	Mp (°C)
a		94	193	**i**		83	157–159
b		81	155–156	**j**		82	179–180
c		85	165–166	**k**		71	160–163
d		83	131–133	**l**		81	181–182
e		88	214–217	**m**		73	171–172
f		65	221–222	**n**		90	153–154
g		81	181	**o**		75	184–185

Table 2 continued

S.no	Arylamide 2	Yield (%)	Mp (°C)	S.no	Arylamide 2	Yield (%)	Mp (°C)
h		88	190–192	**p**		71	198–199

2H, $J = 5.8$ Hz), 7.25 (d, 2H, $J = 6.2$ Hz), 7.56 (d, 2H, $J = 6.2$ Hz), 7.8 (br, 1H), 9.25 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.8, 28.3, 31.1, 45.9, 56.7, 77.3, 109.8, 120.9, 121.5, 124.4, 134.6, 136.1, 156.8, 170.3, 171.5. HRMS *m/z* $[M+Na]^+$ calcd for $C_{22}H_{30}N_4O_4$: 437.2165, Found 437.2151.

Cbz-Phe-Ile-Ala-4-Chloroanilide (**4g**)

White solid, m.p. 231–233 °C, yield 87 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (t, 3H, $J = 7.2$ Hz), 1.18 (d, 3H, $J = 6.6$ Hz), 1.32–1.37 (m, 2H), 1.57 (d, 3H, $J = 6.4$ Hz), 2.34–2.39 (m, 1H), 2.91 (d, 2H, $J = 6.2$ Hz), 3.78 (d, 1H, $J = 5.4$ Hz), 4.51–4.56 (m, 1H), 4.72–4.78 (m, 1H), 5.27 (s, 2H), 5.80 (br, 1H), 6.64 (br, 1H), 7.17–7.55 (m, 14H), 9.65 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.4, 15.8, 18.1, 27.2, 37.4, 38.6, 46.7, 53.4, 56.7, 64.6, 122.8, 125.2, 126.8, 127.4, 128.1, 129.4, 129.9, 134.2, 137.9, 140.5, 142.3, 155.4, 167.8, 170.5. HRMS *m/z* $[M+Na]^+$ calcd for $C_{32}H_{37}ClN_4O_5$: 615.235, Found 615.2348.

Boc-Gly-Ala-Ile-Alilide (**4h**)

White solid, m.p. 240–241 °C, yield 78 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.84 (t, 3H, $J = 5.2$ Hz), 1.09 (d, 3H, $J = 6.4$ Hz), 1.21–1.26 (m, 2H), 1.37 (s, 9H), 1.45 (d, 3H, $J = 6.8$ Hz), 2.41–2.47 (m, 1H), 3.57 (s, 2H), 4.35 (d, 1H, $J = 7.2$ Hz), 4.82–4.87 (m, 1H), 5.23 (br, 1H), 6.82 (br, 1H), 7.15–7.35 (m, 5H), 10.23 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 12.5, 14.8, 17.4, 25.2, 28.3, 37.8, 43.1, 47.5, 55.9, 79.1, 121.2, 124.5, 129.4, 135.3, 156.7, 169.4, 171.5. HRMS *m/z* $[M+Na]^+$ calcd for $C_{22}H_{34}N_4O_5$: 457.2427, Found 457.2454.

Z-Ala-7-Amino-3-Methyl Coumarin Amide (**5a**)

Gum, yield 70 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.35 (d, 3H, $J = 6.8$ Hz), 1.87 (s, 3H), 4.32 (m, 1H), 5.27 (s, 2H), 6.31 (br, 1H), 7.21–7.35 (m, 9H), 8.82 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 16.8, 17.5, 53.7, 66.1, 112.7, 116.3, 118.5, 124.7, 126.9, 127.5, 127.9, 128.6, 137.3, 139.4, 140.7, 151.4, 156.7, 163.1. HRMS *m/z* $[M+Na]^+$ calcd for $C_{21}H_{20}N_2O_5$: 403.127, Found 403.1265.

Fmoc-Leu-7-Amino-3-Methyl Coumarin Amide (**5b**)

Gum, yield 74 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (d, 6H, $J = 6.8$ Hz), 1.83–1.86 (m, 3H), 1.95 (s, 3H), 4.47–4.52 (m, 4H), 6.43 (br, 1H), 7.25–7.56 (m, 12H), 8.91 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.3, 21.8, 22.3, 41.4, 46.8, 53.1, 66.7, 112.3, 128.3, 128.8, 137.7, 140.3, 141.5, 143.7, 151.3, 156.7, 161.8, 171.4. HRMS *m/z* $[M+Na]^+$ calcd for $C_{31}H_{30}N_2O_5$: 533.2052, Found 533.2058.

Fmoc-Val-Leu-7-Amino-3-Methyl Coumarin Amide (**5c**)

Gum, yield 69 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.93 (d, 6H, $J = 7.4$ Hz), 1.07 (d, 6H, $J = 7.0$ Hz), 1.87–1.91 (m, 4H), 1.97 (s, 3H), 4.41 (t, 1H, $J = 5.2$ Hz), 4.51–4.55 (m, 2H), 4.72 (d, 2H, $J = 6.4$ Hz), 5.23 (br, 1H), 7.25–7.55 (m, 13H), 8.75 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 16.8, 17.4, 22.6, 23.9, 32.7, 41.5, 48.1, 52.3, 59.4, 68.2, 112.1, 116.3, 117.9, 123.7, 126.5, 127.2, 128.1, 128.6, 129.7, 137.5, 139.0, 141.5, 142.8, 150.1, 156.3, 162.0, 169.3, 171.5. HRMS *m/z* $[M+Na]^+$ calcd for $C_{36}H_{39}N_3O_6$: 632.2737, Found 632.2731.

Z-Phe-Gly-7-Amino-3-Methyl Coumarin Amide (**5d**)

Gum, yield 65 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.87 (s, 3H), 3.12 (d, 2H, $J = 7.0$ Hz), 4.15 (s, 2H), 4.83 (t, 1H, $J = 5.8$ Hz), 5.32 (s, 2H), 6.41 (br, 1H), 7.15–7.29 (m, 13H), 7.39 (s, 1H), 7.42 (d, 1H, $J = 7.4$ Hz), 8.78 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.8, 38.1, 43.4, 55.6, 67.1, 112.3, 117.6, 118.7, 123.9, 126.3, 126.7, 127.1, 127.5, 128.9, 128.6, 129.1, 137.4, 139.1, 140.2, 141.5, 156.3, 169.4, 172.1. HRMS *m/z* $[M+Na]^+$ calcd for $C_{29}H_{27}N_3O_6$: 536.1798, Found 536.1786.

Fmoc-Phe-3-Amino Coumarin Amide (**5e**)

Gum, yield 72 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.87 (d, 2H, $J = 6.4$ Hz), 4.45 (t, 1H, $J = 5.6$ Hz), 4.62 (d, 2H, $J = 6.8$ Hz), 4.81 (t, 1H, $J = 5.6$ Hz), 6.72 (br, 1H), 7.02 (m, 2H), 7.19–7.78 (m, 16H), 8.91 (s, 1H). ^{13}C NMR

(75 MHz, DMSO-d_6) δ: 38.1, 47.4, 55.7, 67.3, 115.4, 120.8, 122.5, 125.1, 126.2, 126.5, 126.8, 127.7, 128.1, 128.4, 128.8, 19.4, 136.2, 138.8, 140.7, 143.5, 150.7, 156.3, 160.1, 171.2. HRMS *m/z* $[M+Na]^+$ calcd for $C_{33}H_{26}N_2O_5$: 553.1739, Found 553.1812.

Z-Leu-3-Amino Coumarin Amide (**5f**)

Gum, yield 70 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.04 (d, 6H, $J = 7.2$ Hz), 1.78–1.83 (m, 3H), 4.42 (t, 1H, $J = 4.8$ Hz), 5.25 (s, 2H), 6.81 (s, 1H), 7.05 (m, 2H), 7.17–7.23 (m, 8H), 8.74 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 22.0, 22.7, 41.4, 53.2, 65.9, 114.8, 121.4, 122.6, 125.3, 126.7, 127.4, 127.8, 128.5, 129.3, 136.2, 140.8, 150.4, 156.3, 159.7, 171.2. HRMS *m/z* $[M+Na]^+$ calcd for $C_{23}H_{24}N_2O_5$: 431.1583, Found 431.1578.

Boc-Ile-4-Amino-2-Methyl Quinaldine Amide (**5g**)

Gum, yield 67 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.95 (t, 3H, $J = 6.2$ Hz), 1.032 (d, 3H, $J = 6.8$ Hz), 1.23 (m, 2H), 1.37 (s, 9H), 2.53 (m, 1H), 2.63 (s, 3H), 4.31 (d, 1H, $J = 7.0$ Hz), 6.32 (s, 1H), 6.81 (br, 1H), 7.43–7.91 (m, 4H), 8.97 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.3, 15.1, 23.8, 25.3, 28.4, 37.2, 58.6, 78.8, 105.7, 118.1, 120.3, 124.1, 128.8, 129.5, 147.2, 148.9, 156.3, 159.1, 171.8. HRMS *m/z* $[M+Na]^+$ calcd for $C_{21}H_{29}N_3O_3$: 394.2107, Found 394.2112.

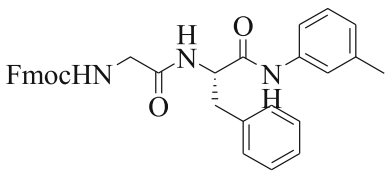
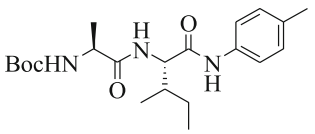
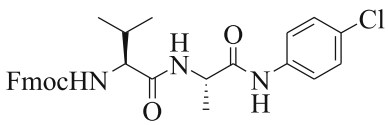
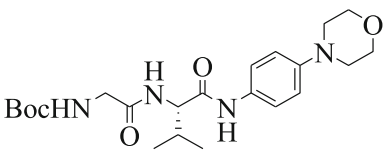
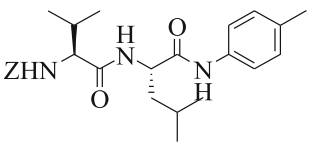
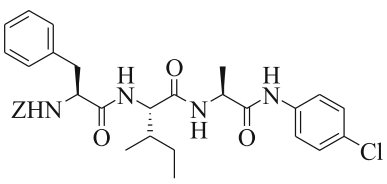
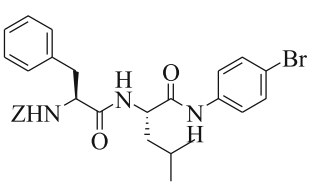
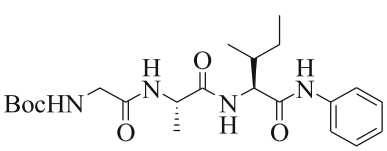
Fmoc-Ala-Phe-4-Amino-2-Methyl Quinaldine Amide (**5h**)

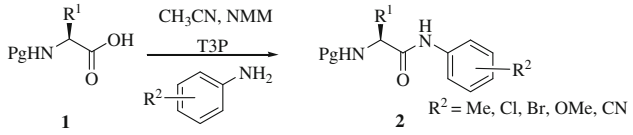
Gum, yield 71 %, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.41 (d, 3H, $J = 5.6$ Hz), 2.43 (s, 3H), 3.12 (d, 2H, $J = 6.8$ Hz), 4.42 (t, 1H, $J = 5.2$ Hz), 4.61 (d, 2H, $J = 7.2$ Hz), 4.81–4.85 (m, 2H), 6.32 (s, 1H), 7.12 (br, 1H), 7.28–7.84 (m, 17H), 8.81 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.1, 25.8, 38.1, 47.0, 51.4, 53.7, 66.4, 106.2, 118.7, 120.7, 124.3, 125.8, 126.7, 127.4, 128.0, 128.5, 128.8, 129.3, 129.7, 129.9, 138.3, 141.2, 143.7, 147.0, 148.2, 156.4, 159.7, 169.7, 172.4. HRMS *m/z* $[M+Na]^+$ calcd for $C_{37}H_{34}N_4O_4$: 621.2478, Found 621.2483.

Results and Discussion

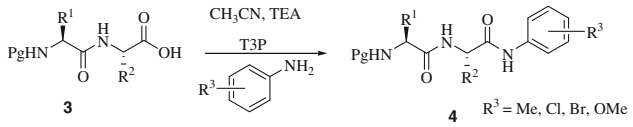
The literature precedence for the preparation of arylamides using T3P illustrated only condensation of Z–Phg–OH and Z–Ala–OH with aniline and pyridine for about 18 h (Dunetz et al. 2011). With our promising results on T3P mediated reactions, we set forth to synthesize arylamides of *N*-protected α-amino/peptide acids in detail. Initially the reaction between

Table 3 List of peptide arylamides **4**

S.no	Peptide arylamide **4**	Yield (%)	S.no	Peptide arylamide **4**	Yield (%)
a		85	**e**		86
b		91	**f**		82
c		93	**g**		87
d		88	**h**		78



Scheme 1 Synthesis of N^{α}-protected amino acid arylamides



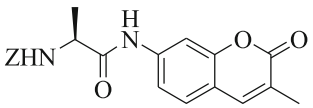
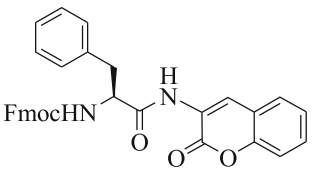
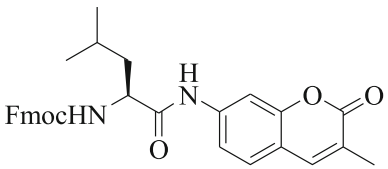
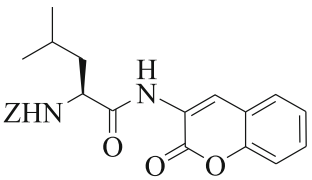
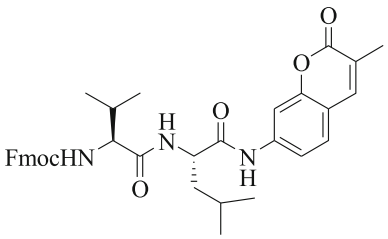
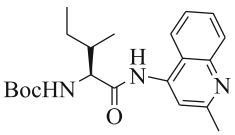
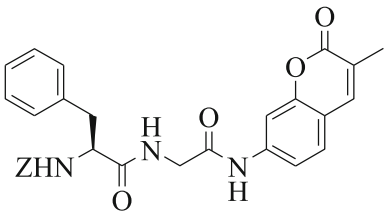
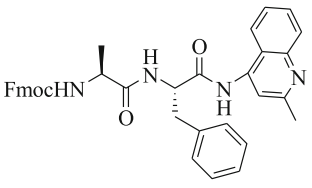
Scheme 2 Synthesis of N^{α}-protected peptide arylamides

Fmoc-Ala-OH **1a** and aniline using T3P was performed. The desired amide **2a** was yielded in 65 % after 18 h. In order to improve the yield and reduce the reaction duration, we further studied the effect of various bases and solvents on reaction outcome. Longer duration was observed for the formation of **2a** with THF and CH_3CN in presence of pyridine (Table 1, entries 2, 3). Whereas the usage of DIPEA with CH_3CN reduces reaction duration to 7 h (Table 1, entry 4). Finally to our delight NMM was found to be the suitable base which reduces the reaction duration drastically (Table 1, entries 5–7). Thus a combination of NMM and CH_3CN mediated by T3P provided satisfactory result in terms of yield and reaction duration (Table 1, entry 7) for arylamidation. In a typical procedure, T3P and NMM were added to a solution of Fmoc-Ala-OH **1a** in CH_3CN at 0 °C, stirred for 10 min, aniline was added to the reaction mixture. After complete consumption of starting materials (1 h), a simple work-up followed by recrystallization with ether afforded pure product **2a** in 95 % yield.

Employing the optimized reaction conditions, a series of N^{α}-protected amino acids were reacted with different substituted aniline derivatives to obtain the corresponding aryl amides in good to excellent yields (Table 2, Scheme 1).

Aryl amides were obtained in excellent yields with aniline derivatives having electron donating groups. Whereas the electron withdrawing groups on aniline derivatives usually lowers the nucleophilicity of amine and

Table 4 List of coumarin arylamides **5**

S. no	Arylamide **5**	Yield (%)	S. no	Arylamide **5**	Yield (%)
a		70	**e**		72
b		74	**f**		70
c		69	**g**		67
d		65	**h**		71

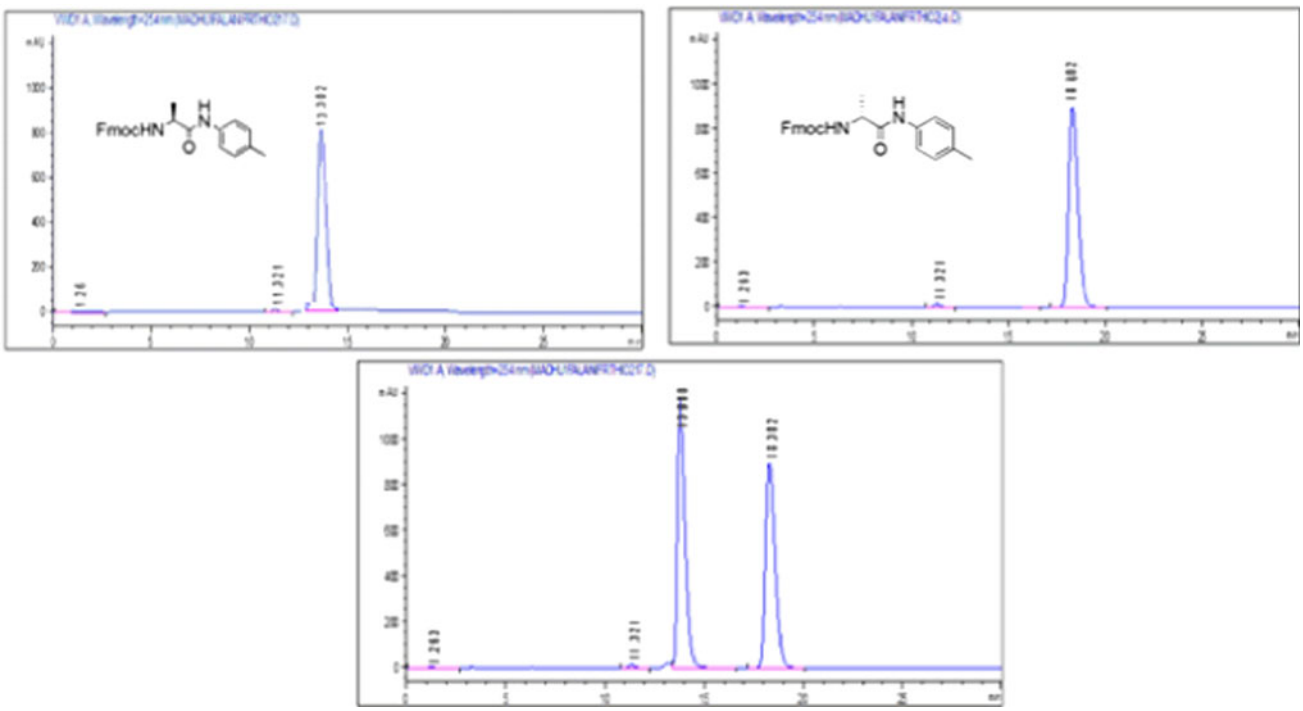


Fig. 1 Chiral HPLC of 2a, 2a* and mixture of 2a and 2a*

thus the corresponding aryl amides were obtained in moderate yield. In general, the reaction worked well even with the sterically hindered amino acids such as Fmoc-Pro-OH, Fmoc-Aib-OH and Fmoc-Val-OH. Additionally, N^{α}-protected hydroxyl amino acids including Ser, Thr and Tyr were also converted to respective aryl amides without protection of the free hydroxy function (**2b, 2c , 2h**). The optimized reaction conditions worked well even for the synthesis of *p*-nitroanilides but with moderate yields.

The protocol was then extended to synthesize several peptide aryl amides. In a typical reaction, the dipeptide Z–Val–Leu–OH **3c** was dissolved in CH_3CN, NMM and T3P were added, the mixture was stirred for 10 min at 0 °C and then *p*-toluedine was added. The desired peptide aryl amide **4c** was obtained in 80 % yield within 1–2 h (Scheme 2, Table 3).

Similar strategy was employed to ligate fluorogenic substrates such as coumarin and quinoline derivatives onto amino acids. Several amine components including 7-amino-3-methyl coumarin (AMC), 3-amino coumarin, 4-amino quinaldine were found to undergo facile amide bond formation with various N^{α}-protected amino/peptide acids in presence of T3P. The pure products were isolated in good yields after column purification (Hexane:EtOAc 80:20, Table 4).

During the course of the study, two enantiomeric N^{α}-protected arylamides derived from Fmoc-L-Ala-OH **2a** and its epimer Fmoc–D–Ala–OH, **2a*** were examined. The chiral HPLC profiles showed single peaks at R_t value 13.30 min **(2a)** and 18.30 min (**2a*)**. Further, the intentionally made mixture of **2a** and **2a*** had two separate peaks corresponding to the L-and D-isomers (R_t = 13.9 and 18.3 min) (Fig. 1). This clearly confirms that the synthesis of arylamides through the present protocol is free from racemization.

Further, peptide arylamides, derived from Fmoc-Phe-(L)-Ala-OH and Fmoc-Phe-(D)-Ala-OH, were prepared and subjected to chiral HPLC analysis. The HPLC profiles reveled single peak at R_t value 9.86 min and 12.06 min. Further, the intentionally made mixture had two separate peaks corresponding to the L-and D-isomers (R_t = 10.04 and 12.44 min) (Fig. 2). This confirms that the protocol employed for synthesis of peptide arylamides is also free from epimerization.

Conclusion

In conclusion, we have developed a facile and an efficient method for the conversion of N^{α}-protected amino/peptide acids into arylamides employing T3P/NMM/CH_3CN system. Unlike most of the earlier protocols which require either multiple steps, hazardous coupling reagents etc., the present approach delivers the product in a most simple and economic way. A series of carboxylic acids including N^{α}-Fmoc/Z/Boc amino/peptide acids have been converted into corresponding arylamides in excellent yields under mild condition. Further arylamides from chromogenic coumarin,

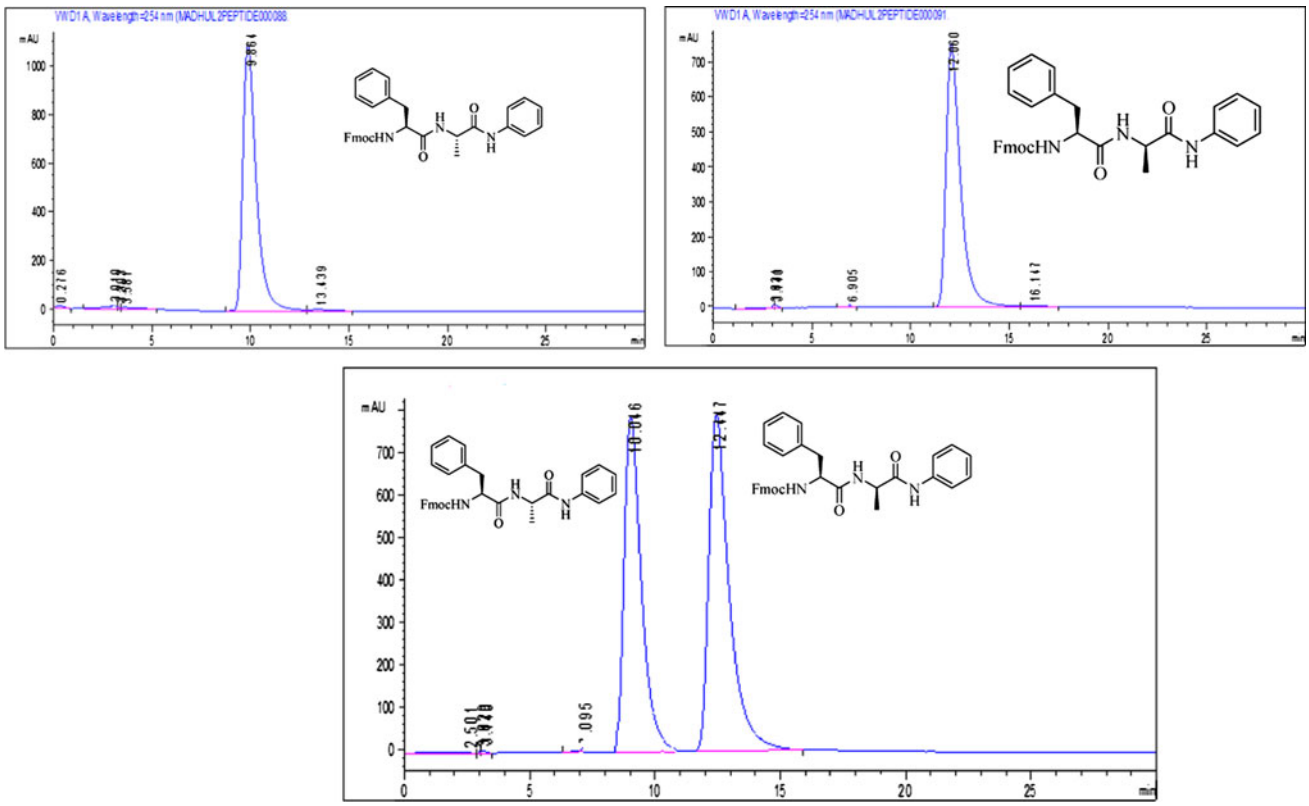


Fig. 2 Chiral HPLC of peptide arylamide

quinalidine and *p*-nitro anilides were also realized in good yields.

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Conflict of interest Chilakapati Madhu, Nageswara Rao Panguluri, Narendra N and Vommina V Sureshbabu declare that they have no conflict of interest.

Statement of informed consent Authors declare that there is no informed consent in the article.

Statement of human and animal rights This article does not contain any studies with human or animal subjects performed by the any of the authors.

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