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A convenient, large-scale synthesis of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines

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Abstract—A large-scale synthesis of a series of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines is described. This method features mild reaction conditions and high chemical yields from commercially available *N*-Boc-2′,6′-dimethyl-L-tyrosine methyl ester.

1. Introduction

Dimethyl-L-tyrosine (Dmt) is an unnatural amino acid that has been widely used in the development of highly selective and potent opioid receptor (OR) agonists and antagonists.[1] The substitution of Dmt for the N-terminal tyrosine (Tyr) in opioid peptides generally increases δ/μ receptor binding affinities, and also enhances δ antagonist potencies.[2] However, a liability of the phenolic moiety of Tyr related compounds is their propensity for metabolism.[3] Recent studies demonstrated that the bioisosteric $CONH_2$ replacement of the phenolic OH in non-peptide cyclazocine opiate analogues displayed comparable OR binding affinities and bioactivities.[4] We envisioned such a bioisosteric replacement could be applied for the phenol moiety of both Tyr and Dmt in peptide related OR ligands. Although the carboxamido analog of Tyr has been made, we first disclosed the synthesis of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines, and their derivatives as opioid receptor modulators, in a PCT patent application with biological activities disclosed.[5] For example, the Ki's for compound **A** (Fig. 1) are 0.06 and 1.44 nM for delta and mu opioid receptors, respectively. During the preparation of this article, the carboxamido for phenol replacement of the Tyr residue has been successfully applied to surrogates for Tyr in opioid peptide ligands.[6] In this paper, we report a convenient, detailed method for scalable preparation of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines from commercially available *N*-Boc-2′,6′-dimethyl-L-tyrosine methyl ester. This general methodology has also enabled us to prepare many substituted 4′-carboxamides from primary to tertiary amines.

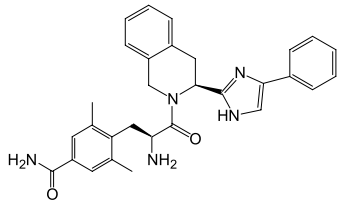

Figure 1. Compound A.

2. Results and discussion

The synthesis of 4-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines was straightforward and is outlined in Scheme 1. Treatment of *N*-Boc-2′,6′-dimethyl-L-tyrosine methyl ester (*N*-Boc-Dmt-OMe) **1** with phenyltriflimide[7] and triethylamine afforded the triflate **2** (99%). The resulting aryl triflate **2** was converted to the aryl carboxylic acid **3** by a palladium-catalyzed carbonylation[8] in the presence of palladium acetate and DPPF (1,1′-bis(diphenylphosphino)-ferrocene) under an ambient CO atmosphere. By monitoring the reaction with LC/MS, we found that the best yield (94%) could be achieved after 8 h at 60 °C.

To selectively convert the aryl acid to the carboxamido intermediates and to avoid the formation of the undesired amide from the methyl ester moiety, Wang and McMurray's method[9] was used. Thus, the primary amide **4a** was successfully prepared by using ammonium chloride

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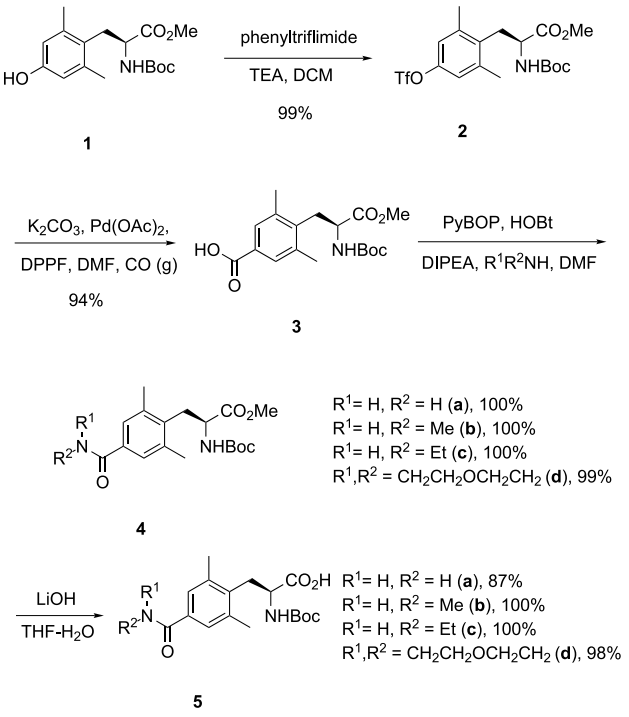

Scheme 1.

as a nitrogen source and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as a coupling agent. In similar methodology, the secondary and tertiary amides **4b–c** were prepared in nearly quantitative yields wherein the corresponding amines were used instead of ammonium chloride. Finally, the resulting amino acid methyl esters **4a–d** were selectively hydrolyzed with lithium hydroxide in a mixture of THF and water at 0 °C and gave the target 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines **5a–d**.

In summary, we have described a convenient, scalable synthesis of several unnatural amino acid derivatives that have been subsequently converted into novel opioid receptor modulators. The potent binding affinities have been disclosed previously.[5] Additional biological activities will be published elsewhere in due course.

3. Experimental

3.1. General

N-Boc-2′,6′-dimethyl-L-tyrosine methyl ester was purchased from RSP Amino Acid, Shirley, MA, USA. PyBOP was purchased from Novabiochem. All other reagents were purchased from Aldrich and used as received. For column chromatography, EMD silica gel 60 (230–400 mesh) was used. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ACS-60.

3.1.1. 4′-Trifluoromethanesulfonyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (2). Into a cool solution of *N*-Boc-Dmt-OMe **1** (7.0 g, 21.6 mmol) and *N*-phenyltrifluoromethanesulfonimide (7.9 g, 22.0 mmol) in DCM (60 mL) was added triethylamine (3.25 mL, 23.3 mmol). The resulting solution was stirred at 0 °C for 1 h and slowly warmed to rt. Upon disappearance of starting materials (monitored by TLC), the reaction was quenched by addition of water. The separated organic phase was washed with 1 N NaOH aqueous solution, water and dried over Na_2SO_4 overnight. After filtration and evaporation, the residue was purified by flash column chromatography (eluent: EtOAc-hexane: 3:7, v/v) to give triflate **2** as colorless gel. 9.74 g, 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.39 (6H, s), 3.06 (2H, d, J=7.7 Hz), 3.64 (3H, s), 4.51–4.59 (1H, m), 5.12 (1H, d, J=8.5 Hz), 6.92 (2H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.3, 28.1, 33.1, 52.2, 53.4, 79.9, 118.7 (q, J=320.5 Hz, CF_3), 120.3, 134.2, 139.8, 147.7, 154.8, 172.7; HRMS(ES$^+$) $[M+H]^+$ calcd. For $C_{18}H_{25}F_3NO_7S$: 456.1304, found, 456.1264; MS(ES$^+$) (relative intensity): 355.8 (100) $(M\text{-Boc})^+$.

3.1.2. 4′-Carboxyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (3). To a suspension of triflate **2** (9.68 g, 21.3 mmol), K_2CO_3 (14.1 g, 0.102 mol), $Pd(OAc)_2$ (0.48 g, 2.13 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (DPPF, 2.56 g, 4.47 mmol) in DMF (48 mL) was bubbled in gaseous CO for 15 min. The mixture was heated to 60 °C for 8 h with CO balloon. The cool mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and filtered. The aqueous layer was separated, acidified with 10% citric acid aqueous solution, extracted with EtOAc, and finally dried over Na_2SO_4. Recrystallization from EtOAc–hexane afforded the acid **3** as a white solid. 7.05 g, 94%; mp 188.0–189.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.42 (6H, s), 3.14 (2H, J=7.4 Hz), 3.65 (3H, s), 4.57–4.59 (1H, m), 5.14 (1H, d, J=8.6 Hz), 7.75 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.6, 28.0, 31.1, 51.7, 52.8, 78.2, 128.4, 128.7, 137.1, 139.7, 155.1, 167.3, 172.2; HRMS(ES$^+$) $[M+H]^+$ calcd. For $C_{18}H_{26}NO_6$: 352.1760, found, 352.1742; MS(ES$^+$) (relative intensity): 251.9 (100) $(M-\text{Boc})^+$.

3.1.3. 4′-Carbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4a). Into a stirring solution of benzoic acid **3** (3.00 g, 8.54 mmol), PyBOP (6.68 g, 12.8 mmol) and HOBt (1.74 g, 12.8 mmol) in DMF (36 mL) was added DIPEA (5.96 mL, 34.2 mmol) and NH_4Cl (0.92 g, 17.1 mmol). The resulting mixture was stirred at rt for 40 min before being partitioned between saturated aqueous NH_4Cl solution and EtOAc. The separated organic phase was washed with 2 N citric acid aqueous solution, saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4 overnight. After concentration, the residue was purified by flash column chromatography (eluent: EtOAc) to give the amide **4a** as a white solid. 3.00 g, 100%; mp 95.5–96.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.39 (6H, s), 3.11 (2H, J=7.2 Hz), 3.65 (3H, s), 4.53–4.56 (1H, m), 5.12 (1H, d, J=8.7 Hz), 5.65 (1H, br s), 6.09 (1H, br s), 7.46 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.6, 28.0, 31.1, 51.7, 52.8, 78.2, 128.4, 128.7, 137.1, 139.7, 155.1, 167.3, 172.2; HRMS(ES$^+$) $[M+H]^+$ calcd. For $C_{18}H_{27}N_2O_5$: 351.1920, found, 351.1869; MS(ES$^+$) (relative intensity): 250.9 (100) $(M-\text{Boc})^+$.

3.1.4. 4′-Methylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4b). Similar method to

preparation of **4a** while methylamine hydrochloride was used instead of NH_4Cl. 100%; white solid; mp 200.5–201.5 °C; ^1H NMR (300 MHz, CD_3CN): δ 1.34 (9H, s), 2.38 (6H, s), 2.85 (3H, d, $J=4.7$ Hz), 3.06 (1H, dd, $J=9.4$, 14.0 Hz), 3.16 (1H, dd, $J=7.9$, 14.2 Hz), 3.63 (3H, s), 4.38 (1H, m), 5.69 (1H, d, $J=8.3$ Hz), 6.88 (1H, s), 7.43 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.7, 26.1, 28.0, 30.9, 51.7, 52.9, 78.2, 126.5, 132.2, 136.7, 137.5, 155.1, 166.5, 172.3; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{19}H_{29}N_2O_5$: 365.2076, found, 365.2101; MS(ES^+) (relative intensity): 365.0 (15) $(M+H)^+$.

3.1.5. 4′-Ethylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4c). Similar method to preparation of **4a** while ethylamine hydrochloride was used instead of NH_4Cl. 100%; white solid; mp 176.0–177.0 °C; ^1H NMR (300 MHz, CD_3CN): δ 1.20 (3H, t, $J=7.2$ Hz), 1.34 (9H, s), 2.38 (6H, s), 3.05 (1H, dd, $J=7.2$, 14.8 Hz), 3.18 (1H, dd, $J=6.4$, 14.0 Hz), 3.36 (2H, m), 3.63 (3H, s), 4.38 (1H, m), 5.96 (1H, d, $J=8.3$ Hz), 6.94 (1H, s), 7.44 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 14.8, 19.8, 28.1, 31.0, 33.9, 51.7, 53.0, 78.3, 126.6, 132.4, 136.7, 137.5, 155.2, 165.8, 172.4; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{20}H_{31}N_2O_5$: 379.2233, found, 379.2190; MS(ES^+) (relative intensity): 379.0 (15) $(M+H)^+$.

3.1.6. 4′-Morpholinylcarbonyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4d). Similar method to preparation of **4a** while morpholine was used instead of NH_4Cl. 99%; white solid; mp 97.0–98.0 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s), 2.37 (6H, s), 3.09 (2H, m), 3.35–3.90 (8H, m), 3.68 (3H, s), 4.54 (1H, m), 5.09 (1H, d, $J=8.4$ Hz), 7.02 (2H, s); ^{13}C NMR (300 MHz, CD_3OD): δ 20.3, 28.7, 33.1, 43.9, 52.7, 54.6, 67.8, 80.6, 127.7, 134.6, 137.9, 139.1, 157.2, 172.7, 174.1; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{22}H_{33}N_2O_6$: 421.2339, found, 421,2373; MS(ES^+) (relative intensity): 421.0 (40) $(M+H)^+$.

3.2. General procedure for hydrolysis of amino acid methyl esters 4a–d

Into an ice-cooled solution of methyl ester **4** (8.54 mmol) in THF (50 mL) was added an aqueous LiOH solution (1 N, 50 mL) and stirred at 0 °C. Upon disappearance of starting materials (monitored by TLC), the organic solvents were removed and the aqueous phase was neutralized with cooled 1 N HCl at 0 °C, and extracted with EtOAc, finally dried over Na_2SO_4 overnight. Filtration and evaporation to dryness led to the acid **5**.

3.2.1. 4′-Carbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5a). White solid; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (9H, s), 2.32 (6H, s), 2.95 (1H, dd, $J=8.8$, 13.9 Hz), 3.10 (1H, dd, $J=6.2$, 14.0 Hz), 4.02–4.12 (1H, m), 7.18–7.23 (2H, m), 7.48 (2H, s), 7.80 (1H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.8, 28.0, 31.2, 53.1, 78.0, 126.9, 131.7, 136.6, 138.3, 155.2, 167.8, 173.4; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{17}H_{25}N_2O_5$: 337.1763, found, 337.1780; MS(ES^+) (relative intensity): 236.9 (6) $(M-Boc)^+$.

3.2.2. 4′-Methylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5b). 100%; white foam; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (9H, s), 2.32 (6H, s), 2.74 (3H, d, $J=4.5$ Hz), 2.94 (1H, dd, $J=6.0$, 14.4 Hz), 3.10 (1H, dd, $J=6.5$, 14.1 Hz), 4.02–4.12 (1H, m), 7.21 (1H, d, $J=8.4$ Hz), 7.44 (2H, s), 8.27 (1H, d, $J=4.5$ Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.1, 26.1, 28.0, 31.2, 53.1, 78.0, 126.5, 132.0, 136.7, 138.1, 155.2, 166.6, 173.4; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{18}H_{27}N_2O_5$: 351.1920, found, 351.1909; MS(ES^+) (relative intensity): 351.0 (15) $(M+H)^+$.

3.2.3. 4′-Ethylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5c). 100%; white foam; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.10 (3H, t, $J=7.2$ Hz), 1.31 (9H, s), 2.33 (6H, s), 2.94 (1H, dd, $J=6.0$, 14.4 Hz), 3.10 (1H, dd, $J=6.0$, 14.1 Hz), 3.30–3.23 (2H, m), 4.04–4.11 (1H, m), 7.17 (1H, d, $J=8.4$ Hz), 7.45 (2H, s), 8.30 (1H, t, $J=5.4$ Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 14.8, 20.0, 28.1, 31.3, 33.7, 53.3, 78.0, 126.6, 132.2, 136.9, 138.2, 155.2, 165.9, 173.5; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{19}H_{29}N_2O_5$: 365.2076, found, 365.2099; MS(ES^+) (relative intensity): 365.0 (16) $(M+H)^+$.

3.2.4. 4′-Morpholinylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5d). White foam; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (9H, s), 2.31 (6H, s), 2.93 (1H, dd, $J=9.0$, 14.1 Hz), 3.10 (1H, dd, $J=5.8$, 14.0 Hz), 3.30–3.85 (8H, m), 4.11 (1H, m), 6.99 (2H, s), 7.19 (1H, d, $J=8.7$ Hz); ^{13}C NMR (300 MHz, CD_3OD): δ 18.8, 27.1, 32.0, 42.3, 53.1, 66.3, 78.9, 126.5, 133.6, 136.8, 137.7, 156.1, 171.3, 173.9; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{21}H_{31}N_2O_6$: 407.2182, found, 407.2180; MS(ES^+) (relative intensity): 407.1 (38) $(M+H)^+$.

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