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Synthesis of Benzimidazoles from Amino Acids with Solvent-free Melting Method

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By using low cost and readily available amino acids as the synthetic blocks, a series of 2-aminomethyl-benzimidazole are synthesized with solvent-free melting method. While the condensation of aspartic acid (or asparagine) with *o*-diaminobenzene gives the fluorescent bisbenzimidazole product without amino group *via* the further deamination reaction in the melting reaction system. The condensation reactions between most amino acids and *o*-diaminobenzenes exhibits higher yields of 58 to 86 % (mostly over 66 %), shorter reaction time (5 h) than that previously reported and better tolerance for different functional groups in amino acids. The structures of twenty benzimidazoles with multifunctional groups, including thirteen new compounds, are systematically characterized with FTIR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. These investigations are beneficial to the further researches on their applications in biochemistry, coordination chemistry and organic synthesis intermediates.

Keywords: Benzimidazole, Synthesis, Amino acid, Solvent-free melting method, Condensation.

INTRODUCTION

Due to many different biological activities, such as anti-tumor, antiviral, antifungal, antiinflammatory, antibacterial, antiprotozoal, antihypertensive, anti-HIV, *etc*., benzimidazoles play an important role in medicinal chemistry and biochemistry[1-7]. At the same time, many simple benzimidazoles are key intermediates in organic synthesis. Therefore, more and more interests have been aroused to the synthesis of benzimidazole and its derivatives recently[4-11].

As a kind of natural biological resource with physiological activities, inexpensive amino acids are extensively used in organic synthesis[12-16]. Especially, when they are applied to synthesize benzimidazoles, the products with amino group are excellent ligands in coordination chemistry and asymmetric synthesis[17-21]. Thus, the study on the preparation of benzimidazoles with multifunctional groups using amino acids as starting materials is urgent[21].

However, there are only limited amino acids utilized in the literature[17,21-24]. For all known benzimidazoles directly prepared from amino acids *via* one-step condensation, the synthetic approach is solution reflux method with lower yields and longer reaction time. Usually, the reflux time in HCl solution is over 70 h (even 6-7 days)[17,21,22]. When using the solvent with the higher boiling point, such as glycol, the reaction time can be greatly shortened to about 20 h[21], but more organic solvents are consumed.

Thus, in view of green chemistry, it is necessary to synthesize these 2-amino-methyl-benzimidazoles by an economical and environmental way for future applications. Herein, we investigate the reaction of the more amino acids **1** and *o*-diaminobenzene (or its derivatives) **2** *via* a solvent-free melting method and a series of benzimidazoles **3a-3t** (**Scheme-I**). Especially thirteen new compounds are systematically characterized by m.p., FTIR, UV, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.

EXPERIMENTAL

All the melting points were determined on an X-5 digital melting points apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 33 FT-IR instrument by liquid film method in the absorption range of 4000-400 cm^{-1}. ^{1}H and ^{13}C NMR spectra were obtained in DMSO-d_6 on a Varian DRX-400 MHz spectrometer and tetramethylsilane (TMS) was used as an internal standard. UV absorption peaks were measured by Shimazu UV-2550 ultraviolet absorption detector with dichloromethane as a solvent. Optical rotations were determined with an Autopol IV polarimeter in CH_3CH_2OH in a 10 cm cell. Elemental analysis was performed on a Perkin

Elmer Series II 2400 elemental analyzer. The mass spectra (MS) were recorded on Thermo LCQ DECA XP MAX mass spectrometer. All reagents and solvents were commercially available and used as received.

Typical procedure for the synthesis of compounds 3a-3t: A flame-dried 50 mL flask was charged with 4 mmol amino acid 1 and 5 mmol *o*-diaminobenzene 2, 17.5 % equiv. $SnCl_2$. Then, the reactants were heated to 170 ºC and the reaction was carried out for 5 h. Once the reaction was finished, the mixture was dissolved with alcohol. The pH value of the resulted solution was adjusted to 9-10 with KOH solution to give the crude product, which was purified by flash chromatography on silica gel to afford the samples **3a-3t** for analysis.

(1*H*-benzo[d]imidazol-2-yl)methanamine (Product 3a): Yellowish solid, yield 83 % (38 %[17]); m.p. 139.6-140.4 ºC; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.29 (2H, s, NH_2), 3.96 (2H, s, CH_2), 7.13-7.20 (2H, m, Ar-H), 7.51-7.56 (2H, m, Ar-H), 12.11 (1H, b, NH) [the corresponding lit. data[17]: ^{1}H NMR (300 MHz, D_2O) δ: 3.78 (2H, s, CH_2), 7.38-7.06 (4H, m, Ar-H)]; ESI-MS *m/z* (%): 148 ([M + H]$^+$, 100).

(6-Methyl-1*H*-benzo[d]imidazol-2-yl)methanamine (Product 3b): White solid, yield 84 %; m.p. 114.1-115.4 ºC; UV-visible (CH_3CH_2OH) λ_{max}: 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.91-2.02 (2H, m, NH_2), 2.35 (3H, s, CH_3), 3.82 (2H, s, CH_2), 6.90 (1H, d, *J* = 4.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.31 (1H, d, *J* = 4.0 Hz, Ar-H), 12.10 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 21.67, 47.27, 114.57, 115.08, 123.17, 130.82, 137.62, 138.93, 155.10; IR ($CHCl_3$) ν: 3148, 3048, 2919, 1628, 1561, 1485, 1449, 1278, 862, 803; ESI-MS *m/z* (%): 162 ([M + H]$^+$, 100); Anal. calcd. for $C_9H_{11}N_3$: C 67.06, H 6.88, N 26.07, Found: C 67.21, H 7.01, N 25.99.

(5,6-Dimethyl-1*H*-benzo[d]imidazol-2-yl)methanamine (Product 3c): White solid, yield 86 %; m.p. 135.1-136.9 ºC; UV-visible (CH_3CH_2OH) λ_{max}: 283 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.62 (2H, s, NH_2), 2.25 (6H, s, $2CH_3$), 3.82 (2H, s, CH_2), 7.21 (2H, s, Ar-H), 12.24 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 20.42, 36.82, 104.99, 130.95, 147.50, 166.58; IR ($CHCl_3$) ν: 3339, 3048, 2964, 1608, 1502, 1463, 1441, 1211, 848; ESI-MS *m/z* (%): 176 ([M + H]$^+$, 100); Anal. calcd. for $C_{10}H_{13}N_3$: C 57.09, H 7.48, N 23.98, Found: C 57.10, H 7.35, N 23.89.

(6-Chloro-1*H*-benzo[d]imidazol-2-yl)methanamine (Product 3d): Yellowish solid, yield 66 %; m.p. 160.9-162.9 ºC; UV-visible (CH_3CH_2OH) λ_{max}: 282 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.67-2.03 (2H, m, NH_2), 3.90 (2H, s, CH_2), 7.13 (1H, d, *J* = 8.0 Hz, Ar-H), 7.48 (1H, d, *J* = 8.0 Hz, Ar-H), 7.52 (1H, s, Ar-H), 12.26 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 37.59, 113.26, 114.65, 122.16, 133.49, 144.13, 153.69, 166.99; IR ($CHCl_3$) ν: 3188, 3059, 2969, 2928, 1561, 1446, 1270, 851, 803, 744; ESI-MS *m/z* (%): 180 ([M-H]$^-$, 100); Anal. calcd. for $C_8H_8N_3Cl$: C 52.90, H 4.44, N 23.14, Found: C 52.79, H 4.47, N 23.28.

(S)-1-(1*H*-benzo[d]imidazol-2-yl)-2-(1*H*-imidazol-5-yl)ethanamine (Product 3e): Yellowish solid, yield 70 % (the last step yield is 70 % when by multi-step condensation[24]); m.p. 163.2-165.2 ºC (163-165 °C[24]); ^{1}H NMR (400 MHz, DMSO-d_6- TMS) δ: 1.60-2.04 (2H, m, NH_2), 2.85-3.18 (2H, m, CH_2), 4.29 (1H, t, *J* = 8.0 Hz, CH), 6.72 (1H, s, Ar-H), 7.06-7.16 (2H, m, Ar-H), 7.44-7.51 (2H, m, Ar-H), 7.52 (1H, s, Ar-H); ESI-MS *m/z* (%): 228 ([M + H]$^+$, 100 %).

(S)-2-(1*H*-imidazol-5-yl)-1-(6-methyl-1*H*-benzo[d]-imidazol-2-yl)ethanamine (Product 3f): Yellowish solid, yield 74 %; m.p. 141.5-143.5 ºC; $[\alpha]^{20}_D$ = -30.2º (c 0.039, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.73-2.22 (2H, m, NH_2), 2.40 (3H, s, CH_3), 3.34-3.47 (2H, m, CH_2), 4.85 (1H, t, *J* = 8.0 Hz, CH), 6.92 (1H, s, Ar-H), 7.03 (1H, d, *J* = 8.0 Hz, Ar-H), 7.35 (2H, s, Ar-H), 7.45 (1H, d, *J* = 8.0 Hz, Ar-H), 7.64-7.83 (1H, m, NH), 7.92 (1H, s, Ar-H), 8.35 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 21.67, 30.38, 49.19, 114.92, 116.52, 124.04, 131.86, 135.42, 135.55, 136.46, 137.17, 150.68, 150.71; IR ($CHCl_3$) ν: 3126, 2969, 1625, 1564, 1488, 1446, 1245, 878, 806; ESI-MS *m/z* (%): 240 ([M-H]$^-$, 100); Anal. calcd. for $C_{13}H_{15}N_5$: C 64.71, H 6.27, N 29.02, Found: C 64.65, H 6.36, N 28.93.

(S)-1-(1*H*-benzo[d]imidazol-2-yl)-2-(1*H*-indol-3-yl)-ethanamine (Product 3g): Yellowish solid, yield 58 % (the last step yield is 55 % when by multi-step condensation[24]); m.p. 119.5-121.2 ºC; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.84-2.14 (2H, m, NH_2), 2.97-3.17 (2H, m, CH_2), 4.34 (1H, t, *J* = 8.0 Hz, CH), 6.92-6.96 (1H, m, Ar-H), 7.02-7.07 (2H, m, Ar-H), 7.10-7.15 (2H, m, Ar-H), 7.32 (1H, d, *J* = 8.0 Hz, Ar-H), 7.45-7.59 (3H, m, Ar-H), 10.78-10.91 (1H, m, NH), 12.26 (1H, b, NH); ESI-MS *m/z* (%): 277 ([M + H]$^+$, 100).

(S)-2-(1*H*-indol-3-yl)-1-(6-methyl-1*H*-benzo[d]-imidazol-2-yl)ethanamine (Product 3h): Yellowish solid, yield 59 %; m.p. 124.6-126.3 ºC; $[\alpha]^{20}_D$ = -16.9º (c 0.036, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 221 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) α: 1.51 (2H, s, NH_2), 2.23 (3H, s, CH_3), 2.52-2.56 (1H, m, Ha in CH_2), 2.86-2.91 (1H, m, Hb in CH_2), 4.09-4.19 (1H, m, CH), 6.75-6.81 (2H, m, Ar-H), 6.84-6.91 (2H, m, Ar-H), 7.11-7.23 (3H, m, Ar-H), 7.37 (1H, d, *J* = 8.0 Hz, Ar-H), 10.62-10.74 (1H, m, NH), 12.07 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 21.75, 27.53, 55.17, 109.68, 110.67, 111.85, 112.13, 118.72, 118.86, 121.31, 124.13, 124.80, 127.69, 130.71, 136.54, 136.79, 138.51, 171.94; IR ($CHCl_3$) ν: 3392, 3029, 2969, 1666, 1586, 1457, 1232, 845, 806; ESI-MS *m/z* (%): 289 ([M-H]$^-$, 100); Anal. calcd. for $C_{18}H_{18}N_4$: C 74.46, H 6.25, N 19.30, Found: C 74.39, H 6.29, N 19.28.

(S)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-2-(1*H*-indol-3-yl)ethanamine (Product 3i): Yellow solid, yield 64 %; m.p. 121.5-123.3 ºC; $[\alpha]^{20}_D$ = -19.6º (c 0.036, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 228 nm; ^{1}H NMR (400 MHz, DMSO-d_6- TMS) δ: 1.68 (2H, s, NH_2), 2.51 (6H, s, $2CH_3$), 2.81-2.98 (2H, m, CH_2), 4.14-4.32 (1H, m, CH), 6.97 (1H, d, *J* = 8.0 Hz, Ar-H), 7.04-7.10 (2H, m, Ar-H), 7.21 (2H, s, Ar-H), 7.34 (1H, d, *J* = 8.0 Hz, Ar-H), 7.56 (1H, d, *J* = 8.0 Hz, Ar-H), 10.98 (2H, s, 2NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 19.06, 37.83, 52.51, 110.45, 111.97, 115.71, 117.06, 118.24, 121.33, 124.31, 127.23, 131.73, 133.00, 138.96, 177.43; IR ($CHCl_3$) ν: 3307, 3025, 2924, 2852, 1666, 1592, 1515, 1422, 1214, 867; ESI-MS *m/z* (%): 305 ([M + H]$^+$, 100); Anal. calcd. for $C_{19}H_{20}N_4Br_2$: C 74.97, H 6.62, N 18.41, Found: C 74.89, H 6.69, N 18.50.

(S)-1-(1*H*-benzo[d]imidazol-2-yl)-2-phenylethanamine (Product 3j): Yellowish solid, yield 63 % (the last step yield

is 70 % when by multi-step condensation[24]); m.p. 163.7-165.4 ºC (164-166 °C[24]); ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.92-2.01 (2H, m, NH_2), 2.98-3.05 (2H, m, CH_2), 4.19 (1H, t, *J* = 8.0 Hz, CH), 6.61-6.70 (1H, m, Ar-H), 7.09-7.14 (2H, m, Ar-H), 7.16-7.24 (4H, m, Ar-H), 7.58-7.76 (2H, m, Ar-H), 8.49 (1H, s, NH); ESI-MS *m/z* (%): 238 ([M + H]$^+$, 100).

(S)-1-(6-methyl-1*H*-benzo[d]imidazol-2-yl)-2-phenylethanamine (Product 3k): Yellowish solid, yield 66 %; m.p. 153.3-155.3 ºC; $[\alpha]^{20}_D$ = -20.8º (c 0.031, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.84-2.08 (2H, m, NH_2), 2.38 (3H, s, CH_3-6), 2.91-2.97 (1H, m, Ha in CH_2), 3.21-3.25 (1H, m, Hb in CH_2), 4.19-4.25 (1H, m, CH), 6.93 (1H, d, *J* = 4.0 Hz, Ar-H), 7.11-7.19 (3H, m, Ar-H), 7.21-7.29 (3H, m, Ar-H), 7.31-7.39 (1H, m, Ar-H), 12.17 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 23.77, 30.45, 55.87, 100.59, 104.98, 126.97, 128.67, 130.29, 132.00, 137.00, 145.33, 163.23, 166.62; IR ($CHCl_3$) ν: 3160, 3025, 2924, 1583, 1491, 1448, 1225, 875, 803; ESI-MS *m/z* (%): 252 ([M + H]$^+$, 100); Anal. calcd. for $C_{16}H_{17}N_3$: C 76.46, H 6.82, N 16.72, Found: C 76.37, H 6.78, N 16.84.

(S)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-2-phenylethanamine (Product 3l): White solid, yield 67 %; m.p. 155.3-157.1 ºC; $[\alpha]^{20}_D$ = -24.4º (c 0.030, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 289 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.24-1.46 (2H, m, NH_2), 2.29 (6H, s, $2CH_3$-6), 2.83-3.17 (2H, m, CH_2), 4.08-4.51 (1H, m, CH), 7.05-7.33 (7H, m, Ar-H), 12.28 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 20.45, 33.79, 49.74, 118.58, 120.47, 127.00, 128.44, 130.28, 134.91, 157.11, 164.73; IR ($CHCl_3$) ν: 3374, 3030, 2926, 2855, 1594, 1513, 1451, 1225, 801; ESI-MS *m/z* (%): 266 ([M + H]$^+$, 100); Anal. calcd. for $C_{17}H_{19}N_3$: C 76.95, H 7.22, N 15.84, Found: C 76.99, H 7.30, N 15.78.

(S)-1-(1*H*-benzo[d]imidazol-2-yl)-3-(methylthio)-propan-1-amine (Product 3m): Yellowish solid, yield 75 % (the last step yield is 87 % when by multi-step condensation[24]); m.p. 71.9-73.7 ºC (72-73 °C[24]); ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.61-1.76 (2H, m, NH_2), 1.99-2.13 (5H, m, CH_2, CH_3), 2.57 (2H, t, *J* = 8.0 Hz, CH_2), 4.04-4.15 (1H, m, CH), 7.12-7.24 (2H, m, Ar-H), 7.48-7.68 (2H, m, Ar-H), 12.41 (1H, b, NH-1); ESI-MS *m/z* (%): 222 ([M + H]$^+$, 100 %).

(S)-1-(6-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)propan-1-amine (Product 3n): Yellowish solid, yield 76 %; m.p. 44.3-45.7 ºC; $[\alpha]^{20}_D$ = -30.5º (c 0.026, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.84-1.95 (2H, m, NH_2), 2.00-2.02 (1H, m, Ha in CH_2), 2.04 (3H, s, CH_3), 2.08-2.13 (1H, m, Hb in CH_2), 2.39 (3H, s, CH_3), 2.55 (2H, t, *J* = 8.0 Hz, CH_2), 4.08 (1H, t, *J* = 8.0 Hz, CH), 6.93 (1H, d, *J* = 8.0 Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.36 (1H, d, *J* = 8.0 Hz, Ar-H), 12.13 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 14.86, 21.70, 29.03, 32.43, 48.21, 122.27, 112.47, 124.03, 131.83, 136.43, 139.99, 150.78; IR ($CHCl_3$) ν: 3277, 3036, 2963, 2891, 1603, 15273, 1505, 1466, 11586, 873, 800, 644; ESI-MS *m/z* (%): 236 ([M + H]$^+$, 100); Anal. calcd. for $C_{12}H_{17}N_3S$: C 61.24, H 7.28, N 17.85, Found: C 61.17, H 7.34, N 17.78.

(S)-6-methyl-2-(pyrrolidin-2-yl)-1H-benzo[d]imidazole (Product 3o): Yellowish solid, yield 81 % (the last step yield is 75 % when by multi-step condensation and the three-step total yield is 45 %[23]); m.p. 104.2-105.9 ºC; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.62-1.65 (2H, m, CH_2), 1.72-1.76 (1H, m, Ha in CH_2), 1.88-2.01 (1H, m, Hb in CH_2), 2.06-2.15 (1H, m, NH), 2.37 (3H, s, CH_3), 2.85-3.01 (2H, m, CH_2), 4.29 (1H, t, *J* = 8.0 Hz, CH), 6.91 (1H, d, *J* = 8.0 Hz, Ar-H), 7.24 (1H, s, Ar-H), 7.33 (1H, d, *J* = 8.0 Hz, Ar-H), 12.14 (1H, b, NH) (the data are similar to the reported[23]); ESI-MS *m/z* (%): 202 ([M + H]$^+$, 100).

1-(6-methyl-1*H*-benzo[d]imidazol-2-yl)ethanamine (Product 3p): Yellowish solid, yield 72 %; m.p. 85.6-87.3 ºC; $[\delta]^{20}_D$ = -20.5º (c 0.031, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.43 (3H, d, *J* = 8.0 Hz, CH_3), 1.49-1.99 (2H, m, NH_2), 2.28 (3H, s, CH_3), 4.16-4.24 (1H, m, CH), 7.25-7.34 (3H, m, Ar-H), 8.65 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 20.41, 23.23, 46.12, 115.27, 115.31, 129.85, 130.14, 137.44, 155.40, 158.93; IR ($CHCl_3$) ν: 3183, 3044, 2970, 1672, 1585, 1534, 1448, 1268, 851, 803; ESI-MS *m/z* (%): 176 ([M + H]$^+$, 100); Anal. calcd. for $C_{10}H_{13}N_3$: C 68.54, H 7.48, N 23.98, Found: C 68.45, H 7.43, N 24.07.

(S)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-3-methylbutan-1-amine (Product 3q): Yellowish solid, yield 72 %; m.p. 114.5-115.9 ºC; $[\alpha]^{20}_D$ = -25.0º (c 0.034, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 0.85-0.98 (6H, m, $2CH_3$-10), 1.54-1.59 (1H, m, CH), 1.97-2.05 (2H, m, CH_2), 2.19-2.24 (2H, m, NH_2), 2.38 (6H, s, $2CH_3$), 4.17-4.24 (1H, m, CH), 7.27 (2H, s, Ar-H), 12.06 (1H, b, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 18.86, 20.94, 21.45, 34.87, 53.20, 118.00, 128.24, 135.46, 167.11; IR ($CHCl_3$) ν: 3361, 2923, 2855, 1663, 1514, 1458, 1216, 803; ESI-MS *m/z* (%): 232 ([M + H]$^+$, 100); Anal. calcd. for $C_{14}H_{21}N_3$: C 72.69, H 9.15, N 18.16, Found: C 72.56, H 9.08, N 18.24.

N-methyl-1-(6-methyl-1*H*-benzo[d]imidazol-2-yl)-methanamine (Product 3r): White solid, yield 82 %; m.p. 119.5-121.2 ºC; UV-visible (CH_3CH_2OH) λ_{max}: 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.72 (1H, s, NH), 2.30 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.81 (2H, s, CH_2), 6.93 (1H, d, *J* = 8.0 Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.35 (1H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 21.70, 36.24, 49.45, 114.63, 114.82, 122.91, 130.53, 138.66, 139.48, 154.39; IR ($CHCl_3$) ν: 3194, 3034, 2924, 1663, 1512, 1482, 1446, 1251, 878, 801; ESI-MS *m/z* (%): 176 ([M + H]$^+$, 100); Anal. calcd. for $C_{10}H_{13}N_3$: C 68.54, H 7.48, N 23.98, Found: C 68.51, H 7.55, N 23.83.

4-(2-Amino-2-(6-methyl-1*H*-benzo[d]imidazol-2-yl)ethyl)phenol (Product 3s): Yellow solid, yield 65 %; m.p. 168.3-169.9 ºC; $[\alpha]^{20}_D$ = -21.1º (c 0.040, CH_3CH_2OH); UV-visible (CH_3CH_2OH) λ_{max}: 246 nm; ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 1.70 (2H, b, NH_2), 2.41 (3H, s, CH_3), 2.88-3.30 (2H, m, CH_2), 3.82-4.22 (1H, m, CH), 6.66 (1H, s, OH), 6.89-7.01 (2H, m, Ar-H), 7.37-7.47 (3H, m, Ar-H), 8.02-8.12 (2H, m, Ar-H), 12.56 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 21.70, 37.40, 55.25, 114.82, 115.01, 115.27, 121.50, 123.49, 123.53, 126.08, 131.16, 131.49, 142.02, 156.68, 167.49; IR ($CHCl_3$) ν: 3374, 3110, 3022, 2918, 1665, 1610, 1591, 1512, 1484, 1449, 1251, 804; ESI-MS *m/z* (%): 268 ([M + H]$^+$, 100); Anal. calcd. for $C_{16}H_{17}N_3O$: C 71.89, H 6.41, N 15.72, Found: C 71.72, H 6.36, N 15.85.

1,2-*bis*(6-methyl-1*H*-benzo[d]imidazol-2-yl)ethene (Product 3t): Yellow solid, yield 68 %; m.p. > 300 ºC (m.p. > 300 ºC[25,26]); ^{1}H NMR (400 MHz, DMSO-d_6-TMS) δ: 2.38 (3H, s, CH_3), 2.44 (3H, s, CH_3), 6.90-7.03 (2H, m, 2CH), 7.18-7.41 (4H, m, Ar-H), 7.58-7.71 (2H, m, Ar-H), 12.15 (2H, b, 2NH); ^{13}C NMR (100 MHz, DMSO-TMS) δ: 22.18, 104.99, 129.13, 132.39, 133.35, 137.32, 138.63, 141.72, 154.98; ESI-MS *m/z* (%): 289 ([M + H]$^+$, 100).

RESULTS AND DISCUSSION

Condition optimization: Directly using amino acids as starting materials, the benzimidazoles can be synthesized *via* one-step[21] or multi-step condensation[21,23,24]. Due to the simpler process, there are a lot of reports on the one-step solution condensation in the past years[21]. In this paper, we investigate the one-step melting condensation. When choosing glycine **1a** and *o*-diaminobenzene **2a** as the model substrates, the reaction conditions of this condensation under solvent-free melting state are optimized first (Table-1).

Obviously, when different catalysts, including phosphowolframic acid (PWA), polyphosphoric acid (PPA), are screened (Entries 1-5), only the reaction catalyzed by polyphosphoric acid or $SnCl_2$ can give the anticipated product and the yield using $SnCl_2$ is better (Entry 5). However, there is no synergistic effect between them (Entry 6). Thus, the low cost $SnCl_2$ is selected as the catalyst in the following experiments. Altering the loading of $SnCl_2$ (Entries 5, 7-12), the results show that its best dosage should be 0.175 equiv. (Entry 11).

Increasing the melting temperature and reaction time, the yield of **3a** is obviously increased (Entry 13). When the melting temperature is 170 ºC, the suitable reaction time should be 5 h (Entry 14) and the longer time is disadvantageous (Entry 15). Similarly, the higher temperature is disadvantageous for the condensation also (Entry 16). Even when the reaction temperature is 190 ºC, no anticipated product can be obtained for the carbonization of the reactants (Entry 17).

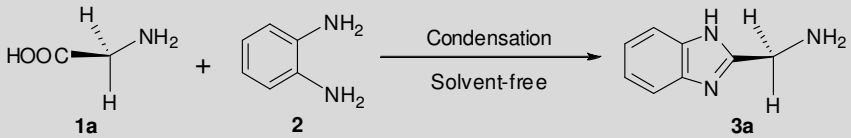
At the same time, the suitable molar feed ratio of *o*-diaminobenzene **2a** and glycine **1a** is investigated. The results (Entries 18 and 19) further show that, neither more nor less glycine **1a** feed ratio is advantageous for the reaction. Therefore, the appropriate synthetic conditions can be summarized as follows: the molar feed ratio (amino acid/*o*-diaminobenzene) 4/5, catalyst 0.175 equiv. $SnCl_2$, 170 ºC and 5 h. Under these conditions, product **3a** is obtained by solvent-free melting method with the best yield of 83 % (Entry 14).

Influences of different substrates: According to the above optimized conditions, the influences of different substrates, including amino acids 1 and *o*-diaminobenzenes 2 are investigated and twenty products are synthesized (Table-2). Among them, thirteen 2-aminomethylbenzimidazoles are new compounds with systematical spectra data.

Obviously, the better yields of some known compounds indicate that the novel one-step method is more efficient than the multi-step condensation[21,23,24]. And compared with the traditional solution reflux method1[7,21,22], our solvent-free melting method also gives higher yields in shorter reaction time. For example, for 2-amino-methylbenzimidazole **3a**, in the literature[17], the reflux reaction time is 72 h and the yield is only 38 %. Herein, the melting reaction time is 5 h and the yield is 83 % (Entry 1).

Furthermore, the product **3a** is synthesized from glycine **1a** with the least steric hindrance of all amino acids, but its

TABLE-1
CONDITION OPTIMIZATION FOR THE CONDENSATION REACTION OF GLYCINE **1a** AND *o*-DIAMINOBENZENE **2a** BY SOLVENT-FREE MELTING METHOD[a]

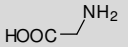
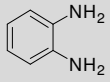
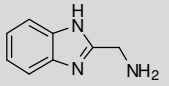
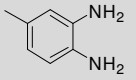
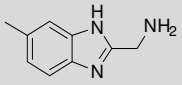
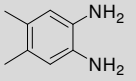
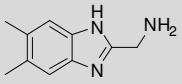
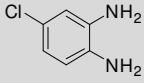
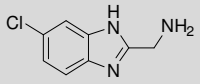
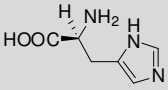
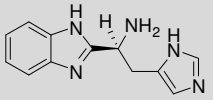
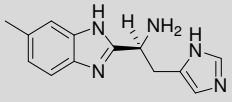
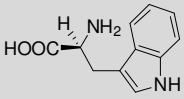
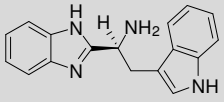
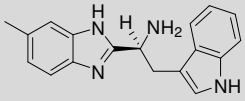
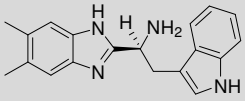
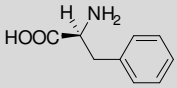
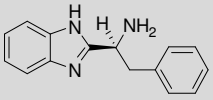
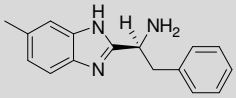
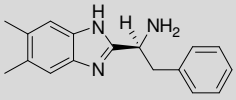
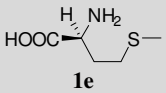
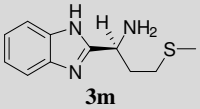
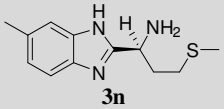
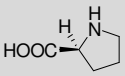
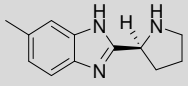


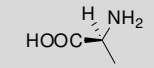
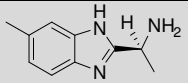
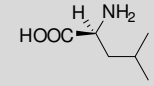
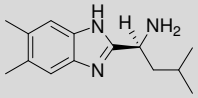
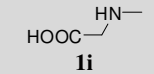
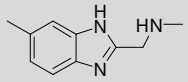
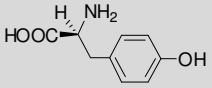
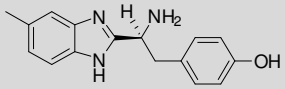
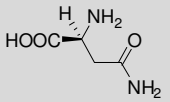
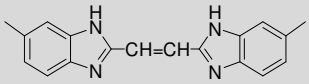
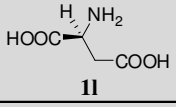
1a **2** **3a**

Entry	Catalyst (equiv.)	Temp. (ºC)	Time (h)	Yield (%)
1	PWA (0.100)	160	3	0
2	Anhydrous CuCl (0.100)	160	3	0
3	$CuCl_2$ (0.100)	160	3	0
4	PPA (0.100)	160	3	40
5	$SnCl_2$ (0.100)	160	3	46
6	PPA/$SnCl_2$ (0.050/0.050)	160	3	33
7	$SnCl_2$ (0)	160	3	0
8	$SnCl_2$ (0.050)	160	3	25
9	$SnCl_2$ (0.075)	160	3	32
10	$SnCl_2$ (0.150)	160	3	62
11	$SnCl_2$ (0.175)	160	3	68
12	$SnCl_2$ (0.200)	160	3	53
13	$SnCl_2$ (0.175)	170	4	79
14	$SnCl_2$ (0.175)	170	5	83
15	$SnCl_2$ (0.175)	170	6	76
16	$SnCl_2$ (0.175)	180	5	56
17	$SnCl_2$ (0.175)	190	5	Carbonization
18[b]	$SnCl_2$ (0.175)	170	5	71
19[c]	$SnCl_2$ (0.175)	170	5	53

[a]Usually using 4 mmol amino acid as starting material, and the molar feed ratio (**1a/2a**) is 4/5 except for special explanation, [b]The molar feed ratio (**1a/2a**) is 3/5, [c]The molar feed ratio (**1a/2a**) is 5/5

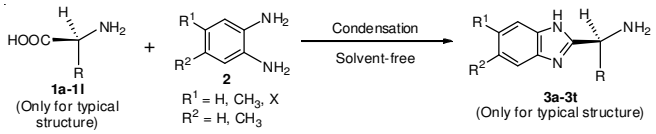
TABLE-2
YIELDS OF TARGET COMPOUNDS **3** WITH DIFFERENT STRUCTURES

Entry	Amino acids 1	Diamines 2 (m.p., ºC)	Products 3	Yield (%)
1	 **1a**	 **2a** (102-103)	 **3a**	83
2	**1a**	 **2b** (87-89)	 **3b**	84
3	**1a**	 **2c** (127-129)	 **3c**	86
4	**1a**	 **2d** (70-74)	 **3d**	66
5	 **1b**	**2a**	 **3e**	70
6	**1b**	**2b**	 **3f**	74
7	 **1c**	**2a**	 **3g**	58
8	**1c**	**2b**	 **3h**	59
9	**1c**	**2c**	 **3i**	64
10	 **1d**	**2a**	 **3j**	63
11	**1d**	**2b**	 **3k**	66
12	**1d**	**2c**	 **3l**	67
13	 **1e**	**2a**	 **3m**	75
14	**1e**	**2b**	 **3n**	76
15	 **1f**	**2b**	 **3o**	81

16	 **1g**	**2b**	 **3p**	72
17	 **1h**	**2c**	 **3q**	72
18	 **1i**	**2b**	 **3r**	82
19	 **1j**	**2b**	 **3s**	65
20[a]	 **1k**	**2b**	 **3t**	65
21[a]	 **1l**	**2b**	**3t**	68

[a]Molar feed ratio (amino acid/diamine **2b**) is 4/10

yield is the highest when using the same *o*-diamino-benzenes **2** (Entries 1 *vs*. 5, 7, 10, 13, or 2 *vs*. 6, 8, 11, 14-16, 18, 19, or 3 *vs.* 9, 12, 17). This not only shows that the bigger steric hindrance from the group R in amino acids (**Scheme-I**) is disadvantageous for the reaction, but also implies that the novel method will be more effective for other amino acids than the traditional solution reflux method.



Scheme-I: Synthetic route of target compounds **3**

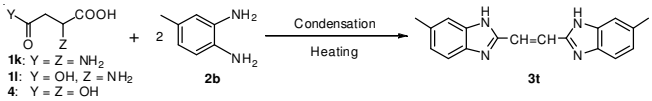
When the same amino acids **1** are used, the results of different diamines **2** show that, the electron-donating methyl in *o*-diaminobenzenes **2** is beneficial to the condensation (Entries 1 *vs*. 2, 5 *vs*. 6, 7 *vs*. 8, 10 *vs*. 11, 13 *vs*. 14). And the more methyl groups, the higher yield (Entries 2 *vs*. 3, 8 *vs*. 9, 11 *vs*. 12). Contrarily, the electron-withdrawing chlorine as the substituent group in *o*-diaminobenzenes **2** can decrease the yield (Entries 1 *vs*. 2). When 4-bromo-benzene-1,2-diamine is used as a diamine, the anticipated product is not obtained, even changing different amino acids **1**.

Of course, the results may be related to not only the electronic effect of different substituents, but also the melting point (m.p.) of the diamine substrates (Table-2, Entries 1-4). For the 4-halobenzene-1,2-diamines **2**, including **2c** and 4-bromobenzene-1,2-diamine (m.p. 62-64 ºC), the lower m.p. makes them easily escape out of the reaction system at 170 ºC melting state. However, the diamine substrate with the higher m.p., 4-nitrobenzene-1,2-diamine (m.p. 199-201 ºC), is also disadvantageous for the reaction and its condensation with different amino acids **1** can not give the expected results.

Thus, usually methyl substituted *o*-diaminobenzenes (**2b** and **2c**) are selected as the diamine substrates to synthesize novel 2-aminomethyl-benzimidazoles (**3**). And more importantly, they are used as the diamine substrates to investigate the tolerance of this solvent-free melting condensation method for different functional groups in amino acids. Table-2 shows that many functional groups, such as hydroxyl, (methyl)amino, methylthio, benzyl, heterocyclic ring, are tolerable with the satisfactory yields (58 to 86 %, mostly over 66 %).

Condensation with subsequent deamination: When asparagine **1k** is used as the substrate, the structure of the product is different from the usually anticipated (**Scheme-I**). Interestingly, a fluorescent bisbenzimidazole **3t** is obtained (**Scheme-II**). The structure of **3t** is confirmed by the test results of ^{1}H NMR, ^{13}C NMR and MS. Furthermore, there is no optical rotation nearly and the result is also consistent with the property of **3t**. When changing the molar feed ratio (**1k/2b**) from 4/5 to 4/10, the increased yield of **3t** is 65 % (Table-2, entry 20).

In literatures[25,26], the synthetic method of fluorescent brightening agent (FBA) **3t** is the condensation of **2b** with maleic acid (the product is *cis*-isomer and the yield is 7.9 %) or 2-hydroxysuccinic acid 4 (the product is *trans*-isomer and the yield is 44.3 %). When the latter starting material **4** (**Scheme-II**) is used, there is a dehydration step[26]. Therefore, on the basis of these experimental results and literatures, it can be seen that during the melting process, the amide group of asparagine **1k** also takes part in the condensation[27,28] and the following reaction is the elimination of ammonia.



Scheme-II: Synthesis of the bisbenzimidazole **3t**

In order to verify the mechanism, especially the formation of double band in **3t** in the later stage, aspartic acid **1l** is used as an amino acid substrate in the solvent-free melting condensation (**Scheme-II**) and the product **3t** is still obtained with the yield of 68 % (Table-2, entry 21). In a word, when aspartic acid **1l** (or asparagine **1k**) is reacted with the *o*-diaminobenzenes **2**, bisbenzimidazole products without amino group can be obtained *via* the normal condensation and the subsequent deamination reaction in the melting reaction system. This may be a novel route to some FBAs with higher yields.

Conclusion

A new route for the synthesis of 2-aminomethyl-benzimidazoles *via* the utilization of amino acids has been developed. The direct solvent-free melting method is finished in one step with shorter reaction time and higher yields than before and bigger tolerance for amino acid substrates. For the amino acids with two carboxyl groups (or similar structure), some functional bisbenzimidazoles also can be formed efficiently. These novel investigations on the synthesis of serial benzimidazoles with multi-functional groups afford a basis for their applications in biochemistry, coordination chemistry and organic synthesis intermediates.

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