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Synthesis and characterization of new benzimidazole derivatives using 2-substituted 1,3-bis(dimethylamino)-trimethinium salts

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ABSTRACT

Novel benzimidazole derivatives are synthesized by the reaction of 2-substituted 1,3-bis(dimethylamino)-trimethinium salts with 2-aminobenzimidazole in the presence of acetic acid or triethylamine in acetonitrile as the solvent. The ultraviolet spectral behavior of these compounds is examined in DMSO.

Benzimidazole derivatives have attracted significant attention as an important class of heterocyclic compounds in the field of chemotherapy and other types of cancer treatment.[1–8] Some of these compounds have also shown antimicrobial activity.[9–13] Because of their broad spectrum of biological activity,[13,14] the benzimidazoles have received significant attention in connection with their synthesis.

Although numerous imidazole derivatives have been synthesized,[15–23] to the best of our knowledge, there are no reports on the synthesis of these derivatives using 2-substituted vinamidinium salts as starting compounds. In this Letter, we describe the synthesis of seven new benzimidazole derivatives using the reaction of 2-substituted 1,3-bis(dimethylamino)-trimethinium salts with 2-aminobenzimidazole, and evaluate their molecular structures on the basis of their ultraviolet (UV) absorption, infrared (IR), ^{1}H, and ^{13}C NMR, as well as mass spectra.

The novel benzimidazole derivatives **2**–**8** were synthesized using a two-step procedure as shown in Scheme 1: (i) synthesis of the 2-substituted vinamidinium salts **1a**–**g** by Vilsmeier–Arnold formylation as described in our previous work;[24–27] and (ii) synthesis of benzimidazole derivatives **2**–**8** using the reaction of the 2-substituted vinamidinium salts **1a**–**g** with 2-aminobenzimidazole in the presence of acetic acid or triethylamine in acetonitrile as the solvent. In acetonitrile, the reaction rate and yield of products were higher in comparison to other solvents. Application of this methodology gave derivatives **2**–**8** in high yields. The products are well-defined, stable solids and have a long shelf-life when stored in an anhydrous environment.

The molecular structures of all seven new derivatives **2**–**8** were confirmed by elemental analysis, IR, ^{1}H, and ^{13}C NMR as well as mass spectra. The UV/vis spectra of **2**–**8** were measured in DMSO. In conclusion, we have established a simple protocol for the efficient synthesis of benzimidazole derivatives **2**–**8** using 2-substituted vinamidinium salts as starting compounds. Clearly, the advantage of this synthetic method is ready preparation of the 2-substituted vinamidinium salts from the corresponding substituted acetic acid under Vilsmeier–Haack conditions.

Typical procedure for the synthesis of benzimidazole derivatives 2–8

Vinamidinium salt **1a**–**g** (1.0 mmol) was dissolved in CH_3CN (5.0 mL) and treated with AcOH (1.0 mL for the synthesis of **2**–**4**) or Et_3N (1.0 mL for the synthesis of **5**–**8**). The resulting solution was heated at 80 °C and 2-aminobenzimidazole (1.0 mmol) in CH_3CN (5.0 mL) was then added dropwise to the stirred mixture. TLC was used to monitor the progress of the reactions. After cooling in a refrigerator, the resulting precipitate was filtered, recrystallized from EtOAc, and dried in vacuo at 80 °C.

3-Bromobenzo[4,5]imidazo[1,2-*a*]pyrimidine (2)

Colorless powder; yield 72%; mp > 250 °C; IR (KBr): 3046, 1689 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ/ppm = 7.56 (t, J = 6.8 Hz, 1H), 7.66 (t, J = 5.6 Hz, 1H), 7.94 (d, J = 8 Hz, 1H), 8.44 (d, J = 8 Hz,1H), 9.18 (d,

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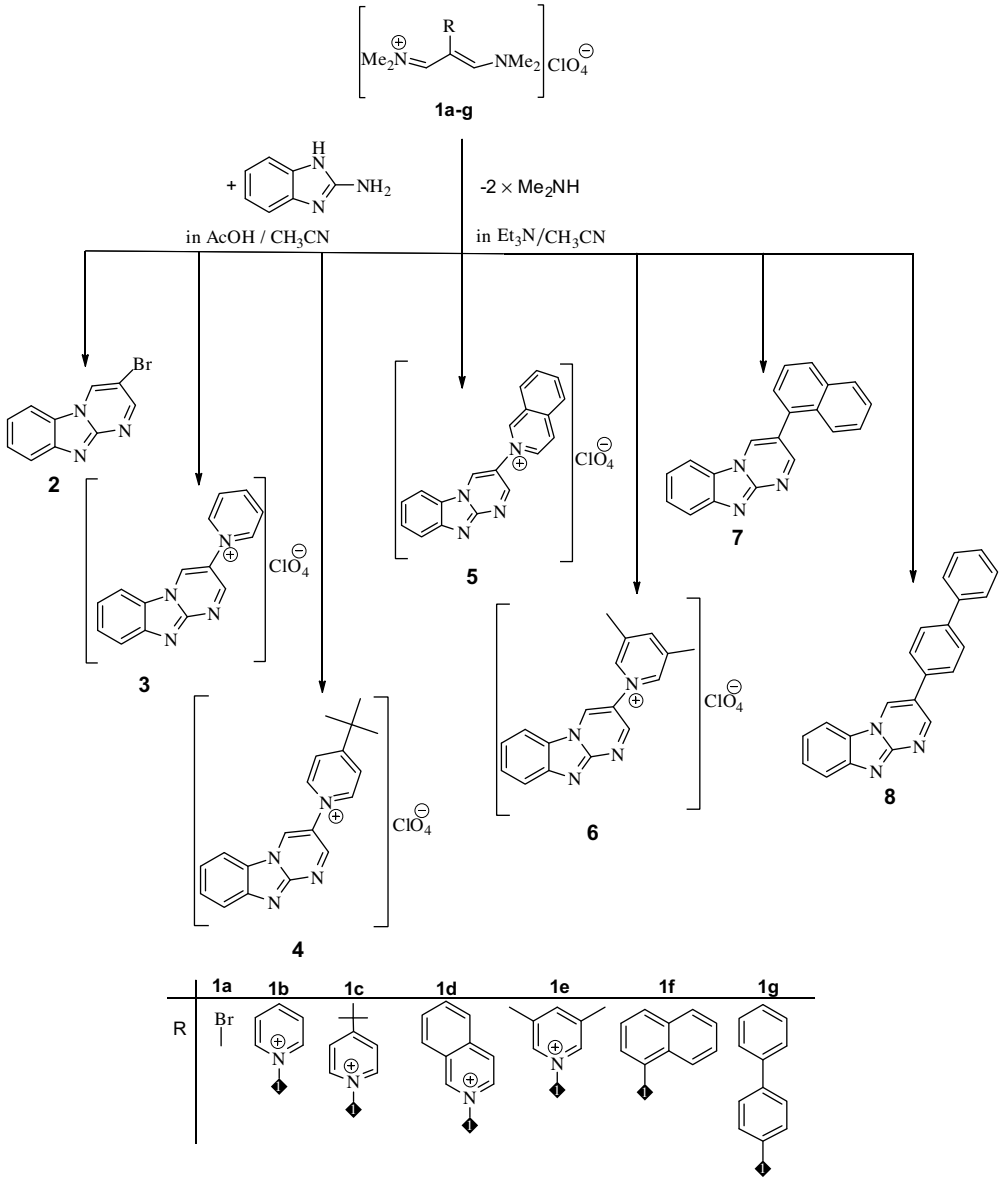

Scheme 1.

J = 2 Hz, 1H), 10.26 (d, J = 2 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ/ppm = 113.7, 117.5, 117.6, 120.2, 123.3, 127.7, 128.1, 143.2, 143.3, 144.8; UV: λ_{max} (DMSO)/nm = 266; EI-MS (70 eV): m/z = 246 [M^+]; Anal. calcd for $C_{10}H_6BrN_3$: C, 48.41; H, 2.44; N, 16.94. Found: C, 47.77; H, 2.21; N, 16.22.

5-(Pyridinium-1-yl)-1-(benzo[4,5]imidazo[1,2-*a*]pyrimidine) perchlorate (3)

Yellow powder; yield 69%; m.p.180 °C; IR (KBr): 3073, 1682, 1090 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ/ppm = 7.23 (dd, J_1 = 6 Hz, J_2 = 3.2 Hz, 1H), 7.36 (dd, J_1 = 6 Hz, J_2 = 3.2 Hz, 1H), 7.61 (m, 1H), 7.71 (m, 1H), 8.47 (dd, J_1 = 8 Hz, J_2 = 6.8 Hz, 2H), 8.91 (m, 1H), 9.30 (d, J = 3.2 Hz,1H), 9.46 (dd, J_1 = 6.4 Hz, J_2 = 1.2 Hz, 2H), 10.36 (d, J = 3.2 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ/ppm = 111.3, 112.9, 120.0, 123.0, 123.1, 127.3, 127.5, 128.2, 134.7, 145.6, 145.7, 147.5, 152.1. UV: λ_{max} (DMSO)/nm = 312; MS: m/z = 247 [M^+–ClO_4^-]. Anal. calcd for $(C_{15}H_{11}N_4)(ClO_4)$: C, 51.96; H, 3.20; N, 16.16. Found: C, 50.78; H, 2.91; N, 16.22.

5-(4-*t*-Butylpyridinium-1-yl)-1-(benzo[4,5]imidazo[1, 2-*a*]pyrimidine)perchlorate (4)

Yellow powder; yield 85%; mp 182–185 °C; IR (KBr): 3036, 1639, 1087 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ/ppm = 1.48 (s, 9H, CH_3), 7.60 (t, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 8 Hz, 1H), 8.51 (d, J = 6.8 Hz, 2H), 9.27(d, J = 2.8 Hz, 1H), 9.36 (d, J = 6.8 Hz, 2H), 10.33 (d, J = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ/ppm = 29.5, 36.8, 112.8, 120.0, 123.0, 125.0, 125.2, 127.2, 127.3, 134.6, 142.8, 144.5, 145.0, 152.2, 152.3. UV: λ_{max} (DMSO)/nm = 312; MS: m/z = 303 [M^+–ClO_4^-]. Anal. calcd for $(C_{19}H_{19}N_4)(ClO_4)$: C, 75.22; H, 6.31; N, 18.47. Found: C, 74.92; H, 6.20; N, 18.11.

5-(Isoquinolinium-2-yl)-2-(benzo[4,5]imidazo[1, 2-*a*]pyrimidine)perchlorate (5)

Brown powder; yield 63%; mp 200 °C; IR (KBr): 3072, 1640, 1085 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ/ppm = 7.62 (t, J = 7.2 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.23 (t, J = 7.2 Hz,

1H), 8.35 (d, J = 8.0 Hz, 1H), 8.44 (t, J = 7.2 Hz, 1H), 8.51(d, J = 8.0 Hz, 1H), 8.65 (d, J = 8.4 Hz, 1H), 8.90 (d, J = 6.8 Hz, 1H), 9.17 (d, J = 6.4 Hz, 1H), 9.40 (d, J = 2.8 Hz, 1H), 10.43 (d, J = 2.8 Hz, 1H), 10.53 (s, 1H); ^{13}C NMR (DMSO-d_6): δ/ppm = 111.3, 112.9, 120.0, 123.0, 123.1, 125.5, 125.8, 127.1, 127.2, 127.3, 127.5, 131.2, 131.9, 135.4, 137.3, 138.3, 144.6, 151.4, 152.1. UV: λ_{max} (DMSO)/nm = 287; MS: m/z = 297[M^+−ClO_4^-]. Anal. calcd for ($C_{19}H_{13}N_4$)(ClO_4): C, 57.51; H, 3.30; N, 14.12. Found: C, 56.87; H, 3.20; N, 14.33.

5-(3,5-Dimethylpyridinum-1-yl)-1-(benzo[4,5]imidazo[1,2-*a*]pyrimidine)perchlorate (6)

Brown powder; yield 78%; mp 220–224 °C; IR (KBr): 3062, 1639, 1067 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ/ppm = 3.23 (s, 6H, CH_3), 7.61 (t, J = 7.2 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.62 (s, 1H), 9.24 (s, 2H), 9.28 (d, J = 2.8 Hz, 1H), 10.35 (d, J = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ/ppm = 18.3, 113.3, 120.5, 123.5, 125.8, 127.8, 127.9, 134.8, 138.7, 142.8, 145.0, 148.6, 149.0, 152.4. UV: λ_{max} (DMSO)/nm = 314; MS: m/z = 275 [M^+−ClO_4^-]. Anal. calcd for ($C_{17}H_{15}N_4$)(ClO_4): C, 54.48; H, 4.03; N, 14.95. Found: C, 54.21; H, 4.30; N, 14.80.

5-(Naphthalene-1-yl)-benzo[4,5]imidazo[1,2-*a*]pyrimidine (7)

Yellow powder; yield 57%; mp 190–194 °C; IR (KBr): 3091, 1687 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ/ppm = 7.45 (t, J = 6.8 Hz, 1H), 7.60 (t, J = 6.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.97–8.19 (m, 7H), 8.41 (d, J = 7.6 Hz, 1H), 8.97 (d, J = 4.4 Hz, 1H), 9.78 (d, J = 4.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ/ppm = 111.3, 113.0, 119.2, 121.5, 122.5, 125.1, 125.6, 126.2, 126.4, 127.0, 127.2, 128.4, 128.5, 128.9, 131.4, 132.0, 133.4, 135.0, 143.9, 157.5. UV: λ_{max} (DMSO)/nm = 288; MS: m/z = 295 [M^+]. Anal. calcd for $C_{20}H_{13}N_3$: C, 81.34; H, 4.44; N, 14.23. Found: C, 81.29; H, 4.70; N, 14.11.

5-[(1,1′-Biphenyl)-4-yl]-benzo[4,5]imidazo[1,2-*a*]pyrimidine (8)

Yellow powder; yield 76%; mp >250 °C; IR (KBr): 3032, 1628, 1486 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ/ppm = 6.91 (dd, J_1 = 5.6 Hz, J_2 = 3.2 Hz, 1H), 7.12 (dd, J_1 = 5.6 Hz, J_2 = 3.2 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.51 (dd, J_1 = 16, J_2 = 7.6 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.78 (d, J = 7.2 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H), 8.47 (d, J = 8.4 Hz, 1H), 9.31 (d, J = 2.4 Hz, 1H), 9.95 (d, J = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ/ppm = 113.1, 119.1, 119.3, 119.6,121.5, 126.2, 127.1, 127.3, 127.4, 127.7, 129.0, 132.4, 132.7, 139.3, 139.7, 143.9, 155.6; UV: λ_{max} (DMSO)/nm = 296; MS: m/z = 321 [M^+]. Anal. calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 81.29; H, 4.80; N, 13.01.

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