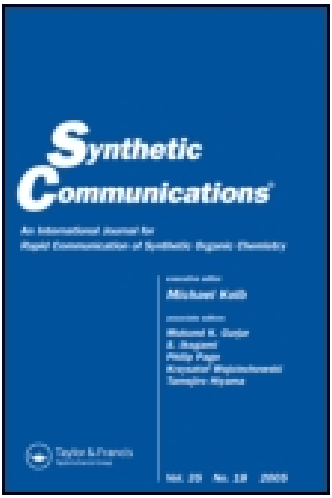

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The Synthesis of New Asymmetric Double Schiff Bases Containing a New o-Amino Benzoic Acid Derivative

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The Synthesis of New Asymmetric Double Schiff Bases Containing a New *o*-Amino Benzoic Acid Derivative

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ABSTRACT

A new *o*-amino benzoic acid derivative, 2-amino-N-phenyl-benzamide, has been obtained by the reaction of *o*-amino benzoic acid and aniline. Twelve new asymmetric Schiff bases, which have both —CH=N— and —C(=O)—NH— functional groups containing 2-amino-N-phenyl-benzamide, have been synthesized and characterized.

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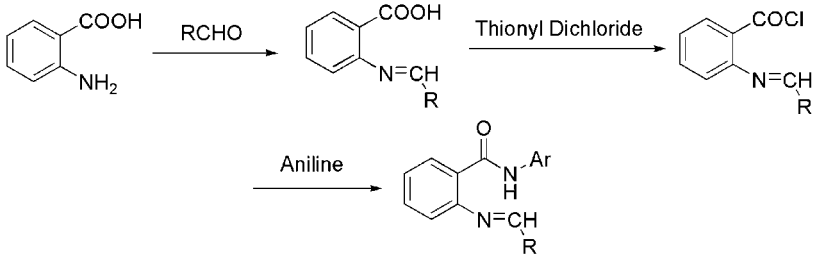
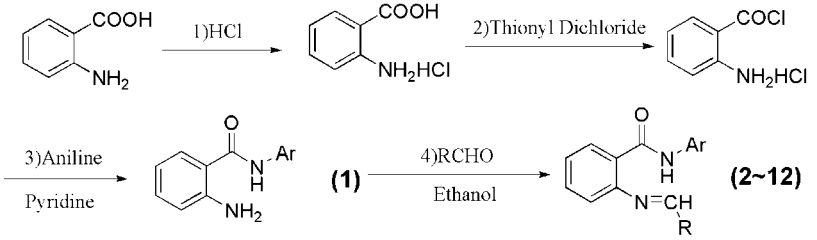


Scheme 1. R = Salicyl, 2-hydroxy-naphaldehyl, p-N,N-dimethyl-benzaldehydehydyl, respectively.

Schiff bases have been extensively studied for their interesting chemistry,[1–3] special physical properties,[4–6] and important biological activity.[7,8] Studies on the synthesis of the asymmetric Schiff bases have received more and more focus. Elder[9] has done some useful work to afford a general route to synthesize unsymmetric Schiff bases as has Atkins.[10] Here we present the design and synthesis of a series of asymmetric double Schiff bases using the 2-amino-N-phenyl-benzamide as the key unit.

Schiff bases with thionyl dichloride were first employed as the route into investigation (Sch. 1), which was eventually confirmed to be unsatisfactory. We found that the unsteadiness of the carbon-nitrogen double bond under reaction conditions was undesirable for further reaction.

Finally, we adopted another synthesis route to obtain the products (Sch. 2). Consequently, the reaction was carried out smoothly, offering the expected products. The preparation of the key intermediate, 2-amino-N-phenyl-benzamide, involved three key steps: (1) the protection of the amido using hydrochloric acid; (2) the preparation of acyl chloride; and (3) the reaction of carboxylic acid halides with aniline. Furthermore, the unsymmetric double Schiff



Scheme 2.

bases were obtained by reaction between 2-amino-N-phenyl-benzamide and aldehydes in presence of a catalytic amount of toluene-*p*-sulfonic acid in ethanol.

According to the experiments, it should be pointed out that the two reactions—steps 1 and 2—could be substituted by the direct reaction between *o*-amino benzoic acid reacted with thionyl dichloride, in which the original acidification step using hydrogen chloride could be omitted. Therefore, the reaction was highly accelerated.

EXPERIMENTAL SECTION

Infrared spectra were obtained on a Perkin-Elmer System 2000 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker BMX-300 MHz. Chemical shifts are indicated in δ values (ppm) downfield from internal TMS. Multiplicities were recorded as s (singlet), d (doublet), t (triplet), br (broad), and m (multiplet). Melting point was obtained with an electrical apparatus and was uncorrected. Elemental analyses were carried out on HP-MOD 1106 microanalyzer. Commercial-grade solvents were used without further purification. Starting materials were purchased from the Aldrich Chemical Company.

Preparation of 2-Amino-N-phenyl-benzamide (1)

o-Amino benzoic acid (0.137 g, 1.0 mmol) in ether (10 mL) was added to fresh thionyl dichloride (10 mL). The resulting mixture was refluxed at 60°C while stirring for 2 hr and then concentrated under reduced pressure to remove solful dichloride. Then the remains were dissolved in ether (20 mL) and added to a solution of aniline (0.186 g, 2.0 mmol) in pyridine (5 mL). The resulting mixture was then refluxed for 3 hr to obtain a green solution. The resulting solution was concentrated under reduced pressure to remove pyridine and ether. Then the mixture was dissolved in 20 mL ethanol and 100 mL distillated water added. The precipitated product, 2-amino-N-phenyl-benzamide (**1**), was obtained. It was recrystallized from ethanol/water (1 : 5). Yield: 50.4%. m.p. 121°C–123°C. ^{1}H NMR: δ 7.7(s, 1H), 7.5(d, 2H), 7.4(d, 1H), 7.3(t, 2H), 7.1(t, 1H), 6.7(m, 3H), 5.3–5.8(br, 2H). IR (KBr): 3471, 3365, 3287, 1638, 1599, 1538, 1441, 1322, 1254, 1156, 943, 751, 692 cm^{-1}. Anal.: $C_{13}H_{12}N_2O$ (212.25): Calcd.: C 73.56, H 5.70, N 13.20. Found: C 73.23, H 5.60, N 13.28.

Preparation of 2-(Benzylideneamino)-N-phenyl-benzamide (2)

To a solution of 2-amino-N-phenyl-benzamide (0.212 g, 1.0 mmol) and a catalysis amount of toluene-*p*-sulfonic acid in 10 mL ethanol, benzaldehyde (0.116 g, 1.1 mmol) in 3 mL ethanol was added drop-wise at room temperature. After 2 min, the crude product appeared as white powder. The mixture was then stirred for 30 min and filtered. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 60.4%. m.p. 214°C–216°C. ^{1}H NMR: δ 8.0(d, 1H), 7.3(m, 2H), 7.2(m, 7H), 7.1(t, 3H), 6.8(t, 1H), 6.6(d, 1H), 6.1(d, 1H). IR (KBr): 3296, 3061, 2830, 1635, 1613, 1510, 1490, 1455, 1392, 1334, 1250, 1160, 1027, 926, 753, 697, 622 cm^{-1}. Anal.: $C_{20}H_{16}N_2O$ (300.35): Calcd.: C 78.98, H 5.37, N 9.33. Found: C 78.66, H 5.36, N 9.28.

Preparation of 2-(2-Methoxy-benzylideneamino)-N-phenyl-benzamide (3)

The procedure was the same as that for **2** and a white powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 77.1%. m.p. 224°C–226°C. ^{1}H NMR: δ 8.0(d, 1H), 7.8(m, 1H), 7.4(t, 2H), 7.2–7.3 (m, 6H), 6.9(t, 1H), 6.8(d, 1H), 6.6(d, 1H), 6.2(s, 1H), 3.8(m, 3H). IR (KBr): 3405, 3047, 2970, 2943, 2842, 1645, 1612, 1493, 1452, 1431, 1328, 1288, 1245, 1189, 1153, 1110, 1024, 950, 862, 831, 750, 695, 635, 583, 525 cm^{-1}. Anal.: $C_{21}H_{18}N_2O_2$ (330.38): Calcd.: C 76.34, H 5.49, N 8.48. Found: C 76.02, H 5.39, N 8.35.

Preparation of 2-(2, 4-Dimethoxy-benzylideneamino)-N-phenyl-benzamide (4)

The procedure was the same as that for **2** and a white powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 48.1%. m.p. 183°C–184°C. ^{1}H NMR: δ 7.9(d, 1H), 7.7(m, 1H), 7.4(m, 2H), 7.3(m, 2H), 7.2(m, 3H), 7.0(m, 1H), 6.8(d, 1H), 6.6(s, 1H), 6.4(m, 1H), 3.9(m, 3H), 3.5(m, 3H). IR (KBr): 3363, 3058, 2936, 2839, 1655, 1612, 1589, 1500, 1459, 1400, 1409, 1291, 1256, 1209, 1158, 1121, 1034, 958, 922, 832, 753, 696, 639, 581 cm^{-1}. Anal.: $C_{22}H_{20}N_2O_3$ (360.41): Calcd.: C 73.32, H 5.59, N 7.77. Found: C 73.21, H 5.40, N 7.75.

Preparation of 2-(3-Chloride-benzylideneamino)-N-phenyl-benzamide (5)

The procedure was the same as that for **2** and a white powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 48.1%. m.p. 212°C–213°C. ^{1}H NMR: δ 8.0(d, 1H), 7.5(m, 1H), 7.4(t, 2H), 7.3(t, 3H), 7.1–7.2(m, 4H), 7.0(t, 1H), 6.6(d, 1H), 6.0(s, 1H). IR (KBr): 3304, 3060, 1636, 1613, 1510, 1487, 1446, 1397, 1294, 1242, 1190, 1116, 949, 911, 885, 858, 795, 697, 643, 593 cm^{-1}. Anal.: $C_{20}H_{15}ClN_2O$ (334.80): Calcd.: C 71.75, H 4.52, Cl 10.59, N 8.37. Found: C 71.58, H 4.19, Cl 10.66, N 8.36.

Preparation of 2-(4-Chloride-benzylideneamino)-N-phenyl-benzamide (6)

The procedure was the same as that for **2** and a white powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 88.7%. m.p. 232°C–234°C. ^{1}H NMR: δ 8.0(d, 1H), 7.6(m, 1H), 7.4(m, 2H), 7.3(m, 4H), 7.2(t, 3H), 6.9(t, 1H), 6.7(d, 1H), 6.1(s, 1H). IR (KBr): 3299, 3061, 2927, 1634, 1614, 1509, 1489, 1448, 1391, 1314, 1249, 1160, 1116, 1089, 1015, 908, 872, 833, 754, 695, 626, 588, 544 cm^{-1}. Anal.: $C_{20}H_{15}ClN_2O$ (334.80): Calcd.: C 71.75, H 4.52, Cl 10.59, N 8.37. Found: C 71.42, H 4.19, Cl 10.70, N 8.31.

Preparation of 2-(4-Dimethylamino-benzylideneamino)-N-phenyl-benzamide (7)

The procedure was the same as that for **2** and an orange powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 45.8%. m.p. 179°C–181°C. ^{1}H NMR: δ 8.0(d, 1H), 7.7(d, 1H), 7.5(d, 2H), 7.4(m, 4H), 7.3(t, 3H), 7.1(t, 1H), 6.7(t, 1H), 6.0(s, 1H), 3.1(s, 6H). IR (KBr): 3299, 3057, 2889, 2807, 1634, 1612, 1503, 1444, 1395, 1351, 1251, 1228, 1188, 1162, 1118, 1055, 1024, 946, 908, 870, 821, 756, 695, 599, 582, 550 cm^{-1}. Anal.: $C_{22}H_{21}N_3O$ (343.42): Calcd.: C 76.94, H 6.16, N 12.24. Found: C 76.52, H 6.09, N 12.35.

Preparation of 2-(2-Hydroxy-benzylideneamino)-N-phenyl-benzamide (8)

The procedure was the same as that for **2** and a white powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 71.4%. m.p. 238°C–240°C. ^{1}H NMR: δ 10.2(d, 1H), 10.0(s, 1H), 8.0(d, 1H), 7.7(t, 1H), 7.6(d, 1H), 7.5(m, 3H), 7.4(m, 4H), 6.7(m, 3H), 6.3(s, 1H). IR (KBr): 3375, 3147, 2868, 2726, 2594, 1630, 1487, 1458, 1432, 1410, 1320, 1285, 1235, 1191, 1156, 1120, 1099, 1076, 1035, 1001, 950, 918, 857, 755, 700, 656, 599, 583, 519 cm^{-1}. Anal.: $C_{20}H_{16}N_2O_2$ (316.35): Calcd.: C 75.93, H 5.10, N 8.86. Found: C 75.68, H 4.93, N 8.78.

Preparation of 2-(2-Hydroxy-3-methoxy-benzylideneamino)-N-phenyl-benzamide (9)

The procedure was the same as that for **2** and a jacinthe powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 69.2%. m.p. 200°C–202°C. ^{1}H NMR: δ 10.3(d, 1H), 10.0(s, 1H), δ 8.0(d, 1H), 7.7(m, 1H), 7.5(m, 2H), 7.4(m, 2H), 7.2(m, 3H), 6.8(m, 2H), 6.6(s, 1H), 6.4(d, 1H), 3.9(m, 3H). IR (KBr): 3446, 3314, 3068, 3017, 2972, 2940, 2844, 1679, 1617, 1598, 1541, 1492, 1461, 1444, 1396, 1322, 1256, 1198, 1134, 1095, 1080, 1039, 972, 892, 859, 835, 784, 761, 736, 695, 589, 544, 505 cm^{-1}. Anal.: $C_{21}H_{18}N_2O_3$ (346.38): Calcd.: C 72.82, H 5.24, N 8.09. Found: C 72.64, H 5.29, N 8.13.

Preparation of 2-(2-Hydroxy-3, 5-dichloro-benzylideneamino)-N-phenyl-benzamide (10)

The procedure was the same as that for **2** and an orange powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 78.7%. m.p. 249°C–251°C. ^{1}H NMR: δ 10.2(d, 1H), 10.0(s, 1H), 8.0(d, 1H), 7.6(m, 1H), 7.4(t, 2H), 7.3(m, 2H), 7.2(t, 3H), 6.8(d, 1H), 6.6(s, 1H), 6.4(d, 1H). IR (KBr): 3391, 3196, 3083, 1641, 1611, 1490, 1463, 1430, 1402, 1314, 1257, 1229, 1193, 1125, 1091, 1031, 1001, 920, 854, 758, 703, 656, 617, 597, 526 cm^{-1}. Anal.: $C_{20}H_{14}Cl_2N_2O_2$ (385.24): Calcd.: C 62.35, H 3.66, Cl 18.41, N 7.27. Found: C 62.34, H 3.29, Cl 18.79, N 7.30.

Preparation of 2-(2-Hydroxy-4-nitryl-benzylideneamino)-N-phenyl-benzamide (11)

The procedure was the same as that for **2** and a yellow powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 56.0%. m.p. 253°C–254°C. ^{1}H NMR: δ 10.2(d, 1H), 10.0(s, 1H), 7.9(d, 1H), 7.7(t, 1H), 7.5(m, 3H), 7.4(m, 2H), 7.2(m, 2H), 7.0(m, 1H), 6.7(m, 2H), 6.3(d, 1H). IR (KBr): 3361, 3034, 1633, 1526, 1492, 1450, 1415, 1333, 1280, 1228, 1155, 1122, 1077, 930, 839, 749, 693, 640, 509 cm^{-1}. Anal.: $C_{20}H_{15}N_3O_4$ (361.11): Calcd.: C 66.48, H 4.18, N 11.63. Found: C 66.32, H 4.09, N 11.65.

Preparation of 2-((2-Hydroxy-naphthalen-yl)-benzylideneamino)-N-phenyl-benzamide (12)

The procedure was the same as that for **2** and a white powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 94.9%. m.p. 238°C–240°C. ^{1}H NMR: δ 10.2(d, 1H), 10.0(s, 1H), 8.1(d, 1H), 7.8(t, 2H), 7.6(m, 4H), 7.5(m, 2H), 7.4(m, 2H), 7.1(m, 2H), 6.8(m, 2H), 6.5(s, 1H). IR (KBr): 3745, 3255, 3193, 3033, 1670, 1620, 1544, 1486, 1442, 1408, 1351, 1319, 1287, 1263, 1210, 1159, 1073, 1040, 979, 895, 750, 691, 596, 511 cm^{-1}. Anal.: $C_{24}H_{18}N_2O_2$ (366.14): Calcd.: C 78.67, H 4.95, N 7.65. Found: C 78.46, H 4.69, N 7.63.

Preparation of 2-((Pyridin-2-yl)-methyleneamino)-N-phenyl-benzamide (13)

The procedure was the same as that for **2** and a white powder was obtained. The crude product was recrystallized from CH_3CN/ethanol (1 : 5). Yield: 63.6%. m.p. 184°C–185°C. ^{1}H NMR: δ 8.6(d, 1H), 8.2(d, 1H), 8.0(m, 2H), 7.6(m, 2H), 7.4(m, 2H), 7.3(m, 4H), 7.2(t, 2H), 7.0(s, 1H). IR (KBr): 3748, 3288, 3059, 1647, 1613, 1508, 1491, 1446, 1402, 1325, 1297, 1246, 1174, 1118, 1080, 1050, 1026, 996, 913, 865, 846, 790, 755, 697, 661, 617, 581, 536, 512 cm^{-1}. Anal.: $C_{19}H_{15}N_3O$ (301.34): Calcd.: C 75.73, H 5.02, N 13.94. Found: C 75.53, H 4.72, N 13.94.

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