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SYNTHESIS OF 2-ARYLBENZIMIDAZOLE ANALOGUES

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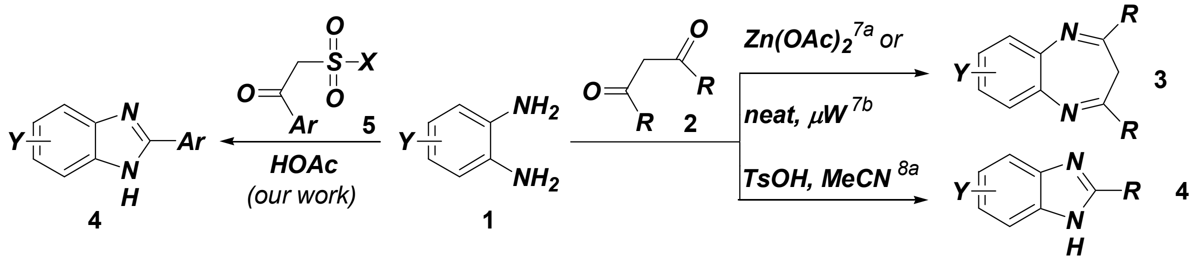
Abstract – Substituted 2-arylbenzimidazoles (**4**) were easily synthesized in good yields starting from the condensation reaction of 1,2-diaminobenzenes (**1**) with β-ketosulfones (**5**) in the presence of boiling HOAc.

Benzimidazole ring system is a key pharmacophore for an increasing important series of nitrogen heterocycles which display a wide range of biological and therapeutic activities.[1,2] A considerable number of attempts have been made to develop the bicyclic benzannulated framework. Transition metal-catalyzed intermolecular or intramolecular cyclization of 2-haloanilides/analogues[3] and condensation of substituted 1,2-diaminobenzenes with benzaldehydes,[4] carboxylic acids,[5] or one-carbon synthons[6] are two main synthetic routes. In most cases, the prepared routes toward 2-arylbenzimidazoles analogues require various oxidative reagents, the participation of strong acids, the involvement of different transition metals, or microwave irradiation.



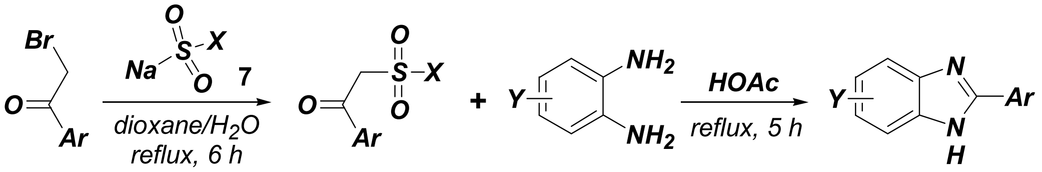
Scheme 1. Synthetic Route toward Substituted 2-Arylbenzimidazoles and Diazepines

Recently, Kidwai reported that $Zn(OAc)_2$ promoted the synthesis of diazepines (**3**) through the reaction of 1,2-diaminobenzenes (**1**) and 1,3-diketones (**2**).[7a] The phenomena of double condensation reaction had been demonstrated by Varma and Leazer under the solvent-free and microwave irradiation conditions (see Scheme 1).[7b] To change the catalytic reaction conditions, Yu and Bao had developed that the synthesis of 2-arylbenzimidazole (**4**) by *p*-TsOH mediated the condensation reaction of 1,2-diaminobenzenes (**1**) and

1,3-diketones (**2**) in MeCN.[8a] The major difference for constructing two frameworks of diazepines (**3**) and 2-arylbenzimidazoles (**4**) was the reaction conditions. To avoid the uncontrollable condensation conditions, β-ketosulfones (**5**) was chosen as a new one-carbon synthon for generating substituted 2-arylbenzimidazoles (**4**). Herein, we would like to describe a facile methodology for synthesizing substituted 2-arylbenzimidazoles (**4**) via the condensation reaction of 1,2-diaminobenzenes (**1**) with β-ketosulfones (**5**) in the presence of boiling HOAc.

β-Ketosulfones (**5**) were easily prepared from the nucleophilic substitution of commercially available 2-bromoacetophenone analogues (**6**, Ar = **a**, Ph; **b**, 4-ClPh; **c**, 4-MeOPh; **d**, 2,5-$(MeO)_2Ph$; **e**, 4-NO_2Ph; **f**, 4-PhPh) with sodium sulfinates (**7**, $NaSO_2X$, X = **a**, Tol; **b**, Ph; **c**, Me) in nearly quantitative yields for 6 h under a boiling co-solvent of 1,4-dioxane and water (v/v = 1/1) condition. Without further purification, condensation of 1,2-diaminobenzenes (**1**) with the resulting β-ketosulfones (**5**) provided substituted 2-arylbenzimidazoles (**4**) in the presence of HOAc at reflux temperature. Adjusting the reaction time, better results were detected in 5 h for the reaction of **1a** with **5a**. To elongate reaction time (20 h), product **4a** provided with only 68% yield. Entries 1~13 showed that ten substituted 2-arylbenzimidazoles (**4a**-**j**) were isolated in 77~90% yields via once purification, as shown in Table 1. The structure of 2-(4-chlorophenyl)-*1H*-benzoimidazole (**4b**) was determined using single-crystal X-ray analysis.[9]

Table 1. Synthesis of Substituted Benzimidazoles (**4**)[a]



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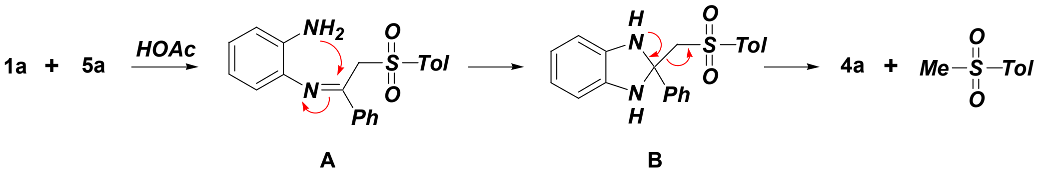
Entry	**6**, Ar =	**7**, X =	**1**, Y =	**4**, yield (%)[b]
1	**6a**, Ph	**7a**, Tol	**1a**, H	**4a**, 86
2	**6a**, Ph	**7b**, Ph	**1a**, H	**4a**, 80
3	**6a**, Ph	**7c**, Me	**1a**, H	**4a**, 82
4	**6b**, 4-ClPh	**7a**, Tol	**1a**, H	**4b**, 78
5	**6c**, 4-MeOPh	**7a**, Tol	**1a**, H	**4c**, 90
6	**6d**, 2,5-$(MeO)_2Ph$	**7a**, Tol	**1a**, H	**4d**, 86
7	**6e**, 4-NO_2Ph	**7a**, Tol	**1a**, H	**4e**, 77
8	**6f**, 4-PhPh	**7a**, Tol	**1a**, H	**4f**, 82
9	—	—	**1b**, 2,3-diaminonaphthalene	**4g**, 80
10	—	—	**1c**, 4,5-Cl_2	**4h**, 82
11	—	—	**1d**, 4,5-Me_2	**4i**, 86
12	—	—	**1e**, 4-CO_2Me	**4j**, 76

[a] The reactions were run on a 5.0 mmol scale with **6** and a 1.0 mmol scale with **1**.

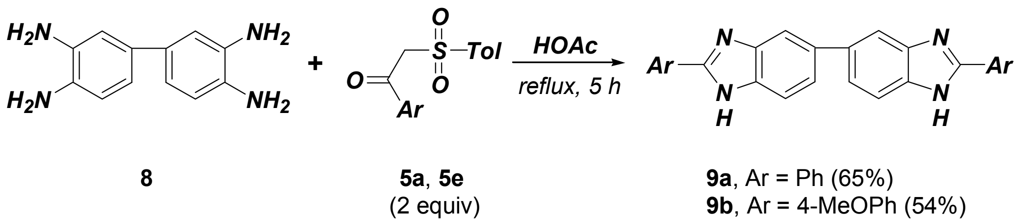
[b] Skeleton **4** was >95% pure as determined by NMR analysis.

For the possible mechanism of **1a** with **5a**, the formation of intermediate **A** was first proposed via the intermolecular condensation process, as shown in Scheme 2. After the intramolecular ring-closure was occurred, intermediate **B** should be generated. Furthermore, by removal of MeSO$_2$Tol, **4a** was formed via carbon-carbon bond cleavage under thermal conditions.[8a]



Scheme 2: Possible Mechanism of 2-Phenylbenzimidazole (**4a**)

Following this protocol, bis-benzimidazoles (**9a-b**) were formed in 65% and 54% yields, respectively via the double condensation of bis-diaminobenzene (**8**) with two equivalents of β-ketosulfones (**5a**) or (**5e**), as shown in Scheme 3.[10] Interestingly, the symmetric bis-benzimidazole skeleton with antitumor activities had been reported as a new class of DNA minor groove binding agents.[10b]



Scheme 3: Synthesis of Substituted Bis-benzimidazoles (**9a-b**)

In summary, we have successfully presented a facile route for the synthesis of 2-arylbenzimidazoles (**4**) via the condensation reaction of 1,2-diaminobenzenes (**1**) with β-ketosulfones (**5**) in the presence of boiling HOAc. Bis-benzimidazoles (**9a-b**) were also prepared by the method. This synthesis begins with simple starting materials and reagents, and provides a new synthetic route toward 2-arylbenzimidazoles.

EXPERIMENTAL

General. THF was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400/200 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an

Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN-OS-Rapid Analyzer or Elementar Vario EL III.

A representative synthetic procedure of 2-arylbenzimidazoles (4) is as follows: Sodium sulfinates (**7**, $NaSO_2X$, 6.0 mmol) was added to a solution of 2-bromoacetophenones (**6**, 5.0 mmol) in co-solvent of 1,4-dioxane and water (20 mL, v/v = 1:1) at rt. The reaction mixture was stirred at reflux for 6 h. The reaction mixture was cooled to rt, concentrated, and partitioned with CH_2Cl_2 (3 x 30 mL) and water (30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude β-ketosulfones (**5**) under reduced pressure in nearly quantitative yields. Without further purification, β-ketosulfones (**5**) (1.05 mmol) was added to a solution of 1,2-diaminobenzenes (**1**, 1.0 mmol) in HOAc (1 mL) at rt. The reaction mixture was stirred at reflux for 5 h. The reaction mixture was cooled to rt, concentrated, and partitioned with EtOAc (3 x 30 mL) and saturated $NaHCO_{3(aq)}$ (30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 1/1) afforded 2-arylbenzimidazoles (**4**).

*2-Phenyl-1H-benzimidazole (**4a**).*[3c] Yield = 86% (167 mg); mp 289-292 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{13}H_{11}N_2$ 195.0922, found 195.0933; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.93 (br s, 1H), 8.20-8.17 (m, 2H), 7.67 (br s, 1H), 7.58-7.47 (m, 4H), 7.22-7.20 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.22, 143.81, 135.00, 130.17, 129.83, 128.95 (2x), 126.43 (2x), 122.52, 121.68, 118.87, 111.32.

*2-(4-Chlorophenyl)-1H-benzimidazole (**4b**).*[3c] Yield = 78% (178 mg); mp 288-290 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{13}H_{10}ClN_2$ 229.0533, found 229.0540; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.99 (br s, 1H), 8.23-8.17 (m, 2H), 7.69-7.56 (m, 4H), 7.22-7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.13 (2x), 134.47 (2x), 129.05 (2x), 128.30, 128.11 (2x), 122.71, 121.88, 118.96, 111.43. Single-crystal X-Ray diagram: crystal of compound (**4b**) was grown by slow diffusion of EtOH into a solution of compound (**4b**) in EtOAc to yield colorless prisms. The compound crystallizes in the orthorhombic crystal system, space group P b c a, a = 9.1642(7) Å, b = 9.7348(7) Å, c = 23.5043(18) Å, V = 2096.9(3) Å^3, Z = 8, d_{calcd} = 1.449 g/cm^3, F(000) = 944, 2θ range 1.733~26.710°, R indices (all data) R1 = 0.0347, wR2 = 0.0743.

*2-(4-Methoxyphenyl)-1H-benzimidazole (**4c**).*[3c] Yield = 89% (199 mg); mp 229-233 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{14}H_{13}N_2O$ 225.1028, found 225.1032; ^{1}H NMR (400 MHz, DMSO-d_6 + $CDCl_3$): δ 12.73 (br s, 1H), 8.13 (d, J = 8.8 Hz, 2H), 7.61 (br d, J = 6.0 Hz, 1H), 7.48 (br d, J = 6.4 Hz, 1H), 7.17-7.13 (m, 2H), 7.09 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ 160.57, 151.36, 143.86, 134.94, 127.98 (2x), 122.67, 121.98, 121.37, 118.40, 114.24 (2x), 110.96, 55.24.

*2-(2,5-Dimethoxyphenyl)-1H-benzimidazole (**4d**).*[10a] Yield = 86% (218 mg); mp 230-234 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{15}H_{15}N_2O_2$ 255.1134, found 255.1139; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (t, *J* = 2.0 Hz, 1H), 7.69-7.67 (m, 2H), 7.66 (br s, 1H), 7.29-7.24 (m, 2H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.98 (s, 1H), 4.03 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.28, 151.36, 149.25, 123.15 (2x), 119.07 (2x), 114.85, 113.15 (2x), 113.04 (3x), 56.51, 56.19.

*2-(4-Nitrophenyl)-1H-benzimidazole (**4e**).*[10b] Yield = 77% (184 mg); mp > 300 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{13}H_{10}N_3O_2$ 240.0773, found 240.0768; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.28 (br s, 1H), 8.43-8.36 (m, 4H), 7.70 (br s, 1H), 7.61 (br s, 1H), 7.27-7.26 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.00 (2x), 147.79, 136.02 (2x), 127.38 (2x), 124.28 (2x), 123.57, 122.42, 119.50, 111.85.

*2-Biphenyl-4-yl-1H-benzimidazole (**4f**).*[10c] Yield = 82% (221 mg); mp 296-300 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{19}H_{15}N_2$ 271.1235, found 271.1242; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.98 (br s, 1H), 8.30-8.28 (m, 2H), 7.89-7.86 (m, 2H), 7.78-7.75 (m, 2H), 7.68 (br s, 1H), 7.56 (br s, 1H), 7.51-7.47 (m, 2H), 7.42-7.38 (m, 1H), 7.23-7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.93, 148.83, 141.27, 139.25, 135.06, 129.14, 129.01 (2x), 127.86, 127.12 (2x), 127.00 (2x), 126.67 (2x), 122.52, 121.73, 118.85, 111.29.

*2-Phenyl-1H-naphtho[2,3-d]imidazole (**4g**).*[5e] Yield = 80% (195 mg); mp 212-216 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{17}H_{13}N_2$ 245.1079, found 245.1083; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.98 (br s, 1H), 8.31-8.28 (m, 2H), 8.03-8.01 (m, 3H), 7.63-7.55 (m, 3H), 7.41-7.32 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.24, 155.36, 144.33, 135.79, 130.67, 130.30, 129.77, 129.03 (2x), 128.07, 127.39, 127.08 (2x), 123.78, 123.04, 115.22, 106.53.

*5,6-Dichloro-2-phenyl-1H-benzimidazole (**4h**).*[5e] Yield = 82% (215 mg); mp 210-213 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{13}H_9Cl_2N_2$ 263.0143, found 263.0148; ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.57 (br s, 1H), 8.05-8.00 (m, 2H), 7.52-7.45 (m, 3H), 7.36 (s, 2H).

*5,6-Dimethyl-2-phenyl-1H-benzimidazole (**4i**).*[5e] Yield = 86% (191 mg); mp 190-192 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{15}H_{15}N_2$ 223.1235, found 223.1241; ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.90 (br s, 1H), 8.04-8.01 (m, 2H), 7.53-7.43 (m, 3H), 7.34 (s, 2H), 2.34 (s, 6H).

*2-Phenyl-1H-benzimidazole-5-carboxylic acid methyl ester (**4j**).*[3g] Yield = 76% (192 mg); mp 196-198 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{15}H_{13}N_2O_2$ 253.0977, found 253.0983; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32-8.31 (m, 1H), 8.13-8.10 (m, 2H), 7.93 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.60 (br s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.42-7.34 (m, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.77, 154.34, 142.75, 138.16, 130.80, 129.10 (2x), 128.91, 127.00 (2x), 124.73, 124.48, 117.02, 115.08, 52.18.

*A representative synthetic procedure of bis-2-arylbenzimidazoles (**9a-b**) is as follows:* β-Ketosulfones (**5a** or **5e**, 1.0 mmol) was added to a solution of bis-diaminobenzene (**8**, 96 mg, 0.45 mmol) in HOAc (1 mL) at rt. The reaction mixture was stirred at reflux for 5 h. The reaction mixture was cooled to rt, concentrated, and partitioned with EtOAc (3 x 30 mL) and saturated $NaHCO_{3(aq)}$ (30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 1/1) afforded products (**9a**-**b**).

*2,2'-Bis-phenyl-1H,1'H-[5,5']bibenzimidazolyl (**9a**).*[11a] Yield = 65% (113 mg); mp > 300 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{26}H_{19}N_4$ 387.1610, found 387.1620; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$): δ12.83 (br s, 2H), 8.17-8.15 (m, 4H), 7.81 (br s, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.51-7.39 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ 151.68 (2x), 136.10 (2x), 129.58 (2x), 129.39 (2x), 128.41 (6x), 126.32 (6x), 122.00 (2x), 114.98 (2x), 112.73 (2x).

*2,2'-Bis-(4-methoxyphenyl)-1H,1'H-[5,5']bibenzimidazolyl (**9b**).*[11b] Yield = 54% (108 mg); mp 269-272 °C (recrystallized from EtOAc); HRMS (ESI, M^++1) calcd for $C_{28}H_{23}N_4O_2$ 447.1821, found 447.1826; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$): δ 8.10 (d, *J* = 8.4 Hz, 4H), 7.76 (br d, *J* = 1.2 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.46 (dd, *J* = 1.2, 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 4H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ 160.57 (2x), 151.80 (2x), 139.29 (2x), 138.30 (2x), 135.77 (2x), 127.90 (4x), 122.07 (2x), 121.58 (2x), 114.75 (2x), 113.87 (4x) , 112.35 (2x), 54.95 (2x).

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9. CCDC 986626 (**4b**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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SUPPLEMENTARY MATERIAL

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