Synthesis of 1,2-Bisubstituted Benzimidazole: 1,3-Shift Mechanism Catalyzed by Acid or Base

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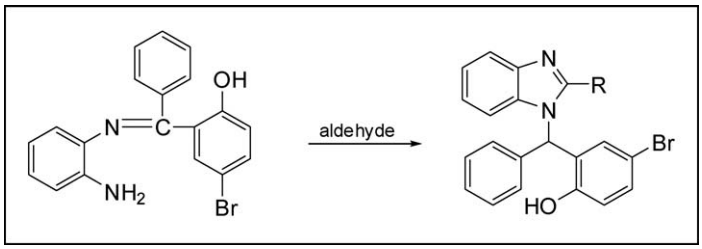

Benzimidazole ring system is a useful nucleus in medicinal chemistry and is found in many biologically active compounds. An efficient approach for the synthesis of 1,2-bisubstituted benzimidazoles is presented in this article, and the mechanism of the condensation from 2-[(2-aminophenylimino)phenylmethyl]-4-bromophenol, using piperdine or acetic acid as catalyst, is studied. 1,3-Shift of negative hydrogen ion is the key step for this rearrangement reaction, and the influences of catalyst, temperature, substrate, and solvent are also investigated.

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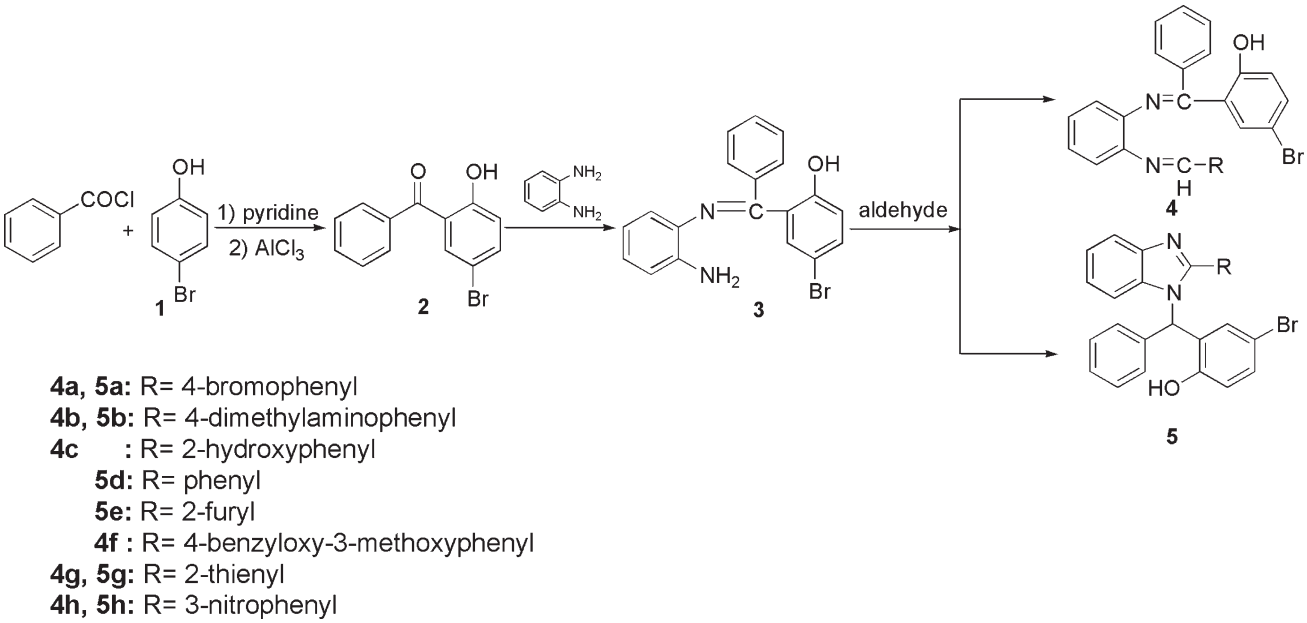
INTRODUCTION

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest [1–4]. In general, nitrogen-containing organic compounds and their metal complexes display a wide range of biological activities [5–8]. Over the past few years, benzimidazole derivatives have been used as anti-inflammatory, analgesic, antifungal and antiviral agents, and thrombin receptor antagonists [9–15]. Apart from the above-mentioned activities, benzimidazoles possess some interesting efficacy of antiallergic, antiproliferative, antitumor, anti-HIV, antibacterial, and antituberculosis activities [16–21]. Because of the broad spectrum of activities reported in the literature so far, the efficient synthesis of important diversely functionalized substituted benzimidazoles has attracted recent attention [22–27]. In particular, the discovery of 1,2-bisubstituted benzimidazoles have increased this interest, which can be attributed not only to their good nucleophilic abilities but their diverse biological and pharmacological properties as well [28]. In our early study of this research, we reported an efficient approach for the synthesis of 1,2-bisubstituted benzimidazoles [29], and surprisingly, we observed the cyclization of di-Schiff bases to benzimidazole derivatives, and such benzimidazole derivatives can also be directly obtained by condensation of aldehydes and mono-Schiff base under refluxing condition. This di-Schiff base may be conveniently prepared at room temperature. However, in refluxing condition, it is converted into the benzimidazole. Their transformations into the corresponding benzimidazoles seemed to rest upon the reaction temperature, but this has turned out to be insufficient for explaining our new findings as only di-Schiff base was obtained in the refluxing condition in certain reactions. To gain better insight into the condensation mechanism to confirm whether di-Schiff base was the intermediate in the formation of benzimidazole, we decided to investigate the reaction of a variety of aldehydes with mono-Schiff base as this would provide more information about the mechanism.

RESULTS AND DISCUSSION

Chemistry. All compounds have been synthesized by the reaction of Schiff base **3** with different aldehydes under three different reaction conditions as follows and providing various compounds in quantitative yield: (A) using piperidine as catalyst by refluxing in ethanol; (B) using acetic acid as catalyst at room temperature in ethanol; and (C) using acetic acid as catalyst by refluxing in ethanol. The condensed products **4** and **5** were purified by recrystallization from a proper solution. The ^{1}H-NMR spectra of the proton on imine C of di-Schiff base appeared at δ 8.0 ppm, whereas disappeared in its

Scheme 1



corresponding benzimidazole ^{1}H-NMR spectrum, and its proton on the asymmetric C shifted upfield to the area of benzene proton and was hardly identified. The precursor Schiff base derivative **3** was synthesized by the condensation of 5-bromo-2-hydroxybenzophenone **2** with 1,2-diaminobenzene, and compound **2** was synthesized by the reaction of benzoic acid 4-bromo-phenyl ester **1** with anhydrous aluminum chloride *via* Fries rearrangement (Scheme 1). Spectral data and elemental analyses of compounds **1–5** fully supported the structures assigned to them, and the structures of compounds **3**, **4c**, and **5g** were further confirmed by X-ray crystallographic analyses (Fig. 1). The results are shown in Table 1.

The results from Table 1 showed that the reaction gave different products because of the reaction conditions and substrates we chose. The aldehydes with small steric hindrance could easily react with Schiff base, and the reaction finished in 3 h in high yield, while 4-benzyloxy-3-methoxy-benzaldehyde on condensation with 2-[(2-aminophenylimino)phenylmethyl]-4-bromophenol gave a very low product yield even at prolonged reaction time. The reaction results were different when catalyst changed, benzimidazole was obtained in the presence of acetic acid and/or a higher reaction temperature, while using piperidine as catalyst, di-Schiff base or no reaction product was obtained.

The mechanism of reaction. A mechanism for the formation of benzimidazole catalyzed by acetic acid was proposed as illustrated in Scheme 2. First, carbonyl group was activated to react with mono-Schiff base 3 directly by the addition of acetic acid. Mono-Schiff base 3 was transformed into di-Schiff base 4 at room temperature. However, higher temperature could bring about an intramolecular rearrangement. The nitrogen atom in the imino group attacked the secondary amine carbon to close the five-membered ring, owing to steric hindrance of the substituents on imino carbon. After 1,3-shift of negative hydrogen ion, benzimidazoles 5 was obtained.

To confirm the reaction mechanism, different solvents such as DMF, EtOH, and toluene were chosen as reaction solvents. Aprotic solvent DMF showed fast reaction rate than nonpolar solvent and protic solvent due to solvent effect, and this result exhibited that the reaction intermediate was charged. Protic solvent EtOH also showed good reaction rate and product yield, this was because benzimidazoles had a poor solubility in EtOH and thus promoted the reaction. A number of experiments were conducted to verify the mechanism. For example, the di-Schiff bases of *m*-nitrobenzaldehyde, *p*-bromobenzaldehyde, and thiophene formaldehyde could be conveniently prepared at room temperature, while the corresponding benzimidazoles can be obtained at higher temperature. Such benzimidazoles could be directly obtained in refluxing condition. However, in none of these cases the formation di-Schiff base was observed. Thus, temperature had significant influence in the reaction, and from the mechanism, we inferred that the two courses are competitive and that the formation of di-Schiff base is reversible.

Another probable mechanism for the formation of benzimidazole catalyzed by piperidine is shown in

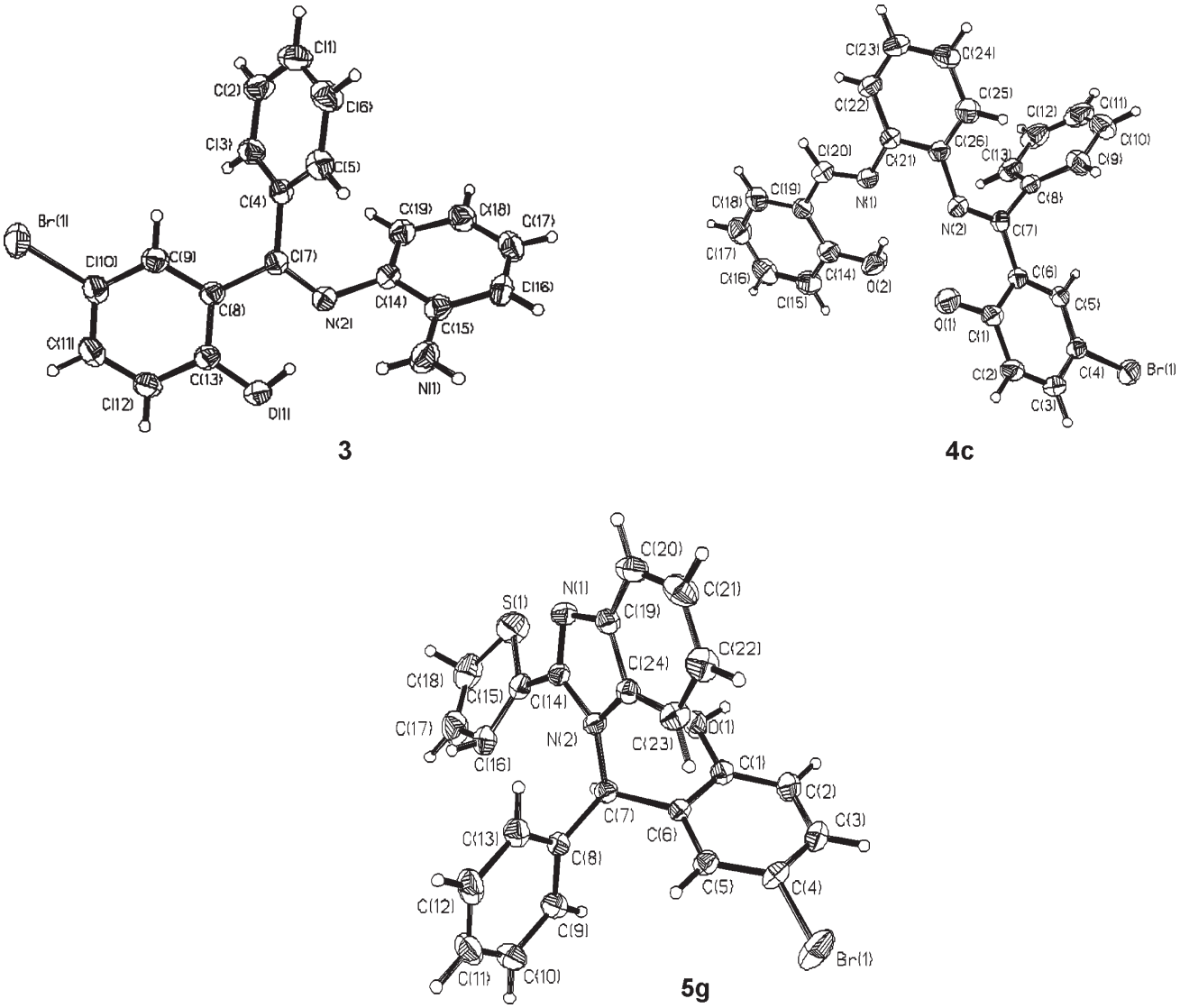


Figure 1. X-ray ORTEP drawings of **3**, **4c**, and **5g**.

Scheme 3. Piperidine first reacted with aldehyde to form quaternary ammonium salt and then condensed with 2-[(2-aminophenylimino) phenylmethyl]-4-bromophenol to obtain di-Schiff base and then rearranged to benzimidazole. The di-Schiff base proved to be the intermediate, as both of the di-Schiff base and benzimidazole were detected in the same reaction.

The substituent on aldehyde had significant impact on the reaction kinetics. Electron-withdrawing substituent such as nitro group and nitrile group could lower the electron density on the oxygen atom on aldehyde group, which could lower the alkalinity and thus lower the reactivity for the condensation. However, when there is more than one activating group on aldehyde, such as 4-benzyloxy-3-methoxy-benzaldehyde and 3,5-dibromo-4-hydroxy-benzaldehyde, side reactions were observed with low yield or even no reaction product. The influence of the position of substituent should also be taken into account. When the phenyl group had a hydroxyl group in the ortho-position, a complex mixture was obtained. The lack of reactivity could be explained by the influence of hydrogen bond that was formed between hydroxyl group and aldehyde group of salicylaldehyde. In some cases, the impact of the site of the substituent was even larger than steric hindrance and catalyst effect.

Finally, to clarify the issue of whether the two courses were competitive and the formation of di-Schiff base was reversible in the presence of acid, the di-Schiff bases were subjected to the acidic refluxing condition to investigate the formation of all possible products (Table 2).

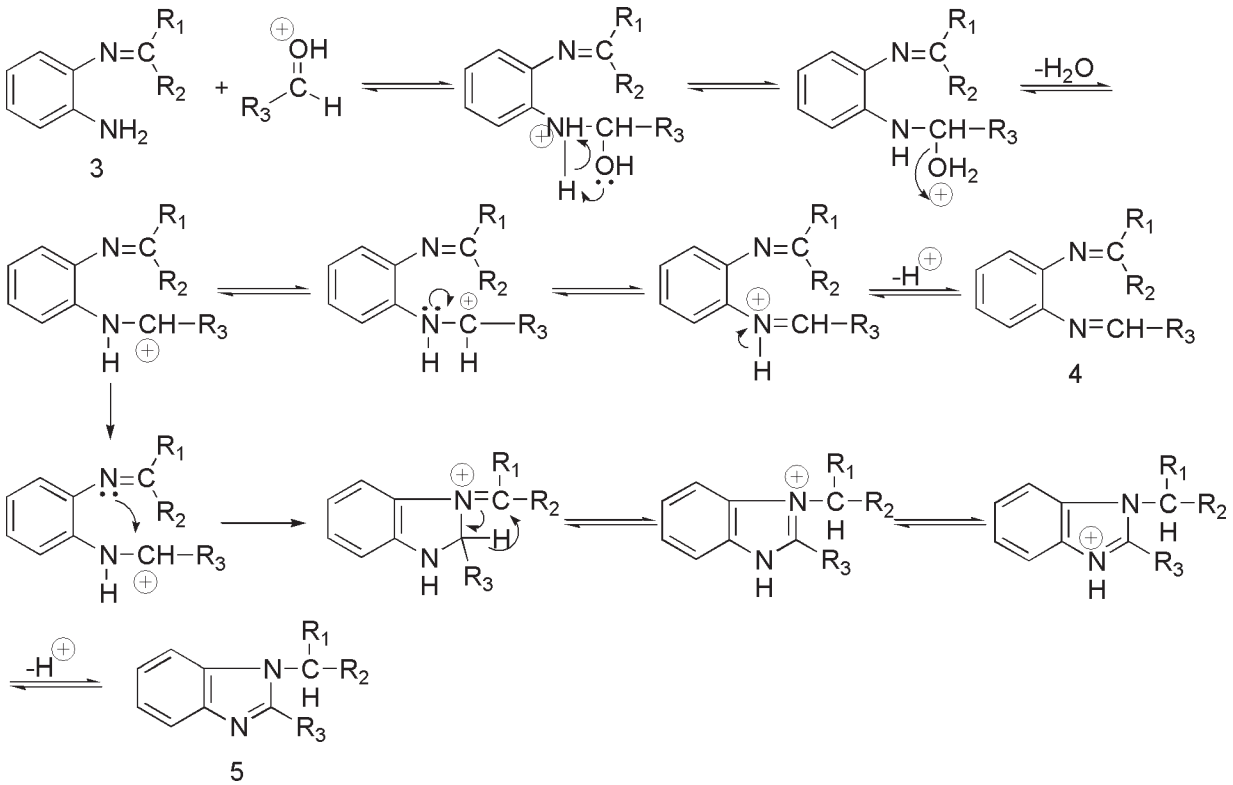
Table 1

Preparation of compounds **4a–h** and **5a–h**.

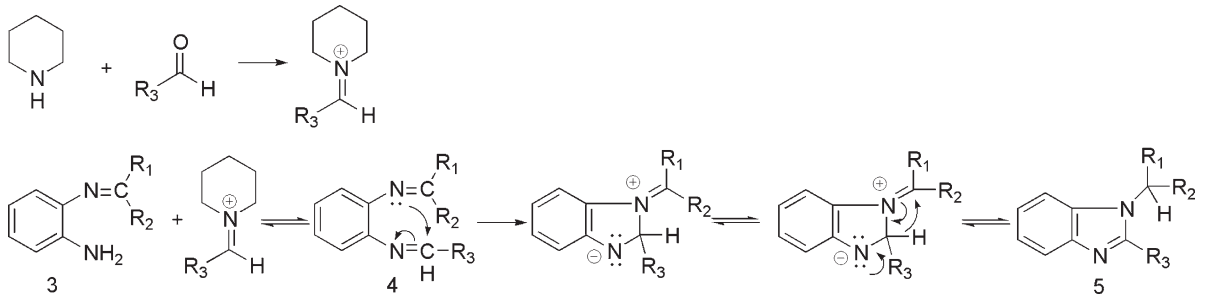
Entry	Substrate	Reaction condition	Yield (%)	Product
1	*p*-Bromobenzaldehyde	A	85	Di-Schiff base **4a**
		B	86	Di-Schiff base **4a**
		C	82	Benzimidazole **5a**
2	*p*-Dimethylaminobenzaldehyde	A	81	Di-Schiff base **4b**
		B	80	Benzimidazole **5b**
		C	86	Benzimidazole **5b**
3	Salicylaldehyde	A	62	Di-Schiff base **4c**
		B		–
		C	66	Di-Schiff base **4c**
4	Benzaldehyde	A	80	Benzimidazole **5d**
		B	83	Benzimidazole **5d**
		C	87	Benzimidazole **5d**
5	Furaldehyde	A	75	Benzimidazole **5e**
		B	70	Benzimidazole **5e**
		C	62	Benzimidazole **5e**
6	4-Benzyloxy-3-methoxy-benzaldehyde	A	43	Di-Schiff base **4f**
		B		—
		C	47	Di-Schiff base **4f**
7	Thiophene formaldehyde	A	88	Di-Schiff base **4g**
		B	84	Di-Schiff base **4g**
		C	89	Benzimidazole **5g**
8	*m*-Nitrobenzaldehyde	A	58	Di-Schiff base **4h**
		B	56	Di-Schiff base **4h**
		C	63	Benzimidazole **5h**

Reaction condition: (A) catalyzed by piperidine in refluxing ethanol; (B) catalyzed by acetic acid at room temperature in ethanol; (C) catalyzed by acetic acid in refluxing ethanol.

Scheme 2



Scheme 3



Interestingly, benzimidazoles were observed in these reactions. Hence, it was reasonable to confirm that there existed two competitive courses in the reaction and that the formation of di-Schiff base was reversible. The aforementioned results strongly favored this mechanism, particularly, if one takes into account our findings that mono-Schiff base and benzimidazole were both found when heated, the di-Schiff base was heated at refluxing in the presence of acetic acid. 4-Bromo-2-{[2-(2-hydroxybenzylideneamino)phenylimino] phenyl methyl}phenol was difficult to transform into benzimidazole because a tetratomic ring was formed through the reaction between the oxygen atom on hydroxyl group and carbocation, thus lowering the electrophilicity of carbocation.

CONCLUSIONS

We have reported an efficient methodology for the synthesis of 1,2-bisubstituted benzimidazoles by using acetic acid and piperidine as catalysts. On this basis, two possible mechanisms have been presented. The mechanism of reaction involved 1,3-shift of negative hydrogen ion. It has been confirmed that there were two competitive courses in the synthesis of benzimidazoles and that the formation of di-Schiff base was reversible in the presence of acid, while di-Schiff base was confirmed to be an intermediate in the presence of piperidine. We also found that the reaction temperature, solvent, and the structures of aldehydes exerted substantial influences on the products.

EXPERIMENTAL

General. Melting points were taken on Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet NEXUS 670 FTIR. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brucker AM-500 MHz spectrometers. HRMS were obtained on a Bruker Daltonics APEXII47e spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF_{254} plates. Single crystal was measured on an Enraf-Nonius CAD-4 diffractometer. Cell refinement: CAD-4 software; data reduction: NRCVAX; program(s) used to solve structure: SHELX97; program(s) used to refine structure: SHELX97; molecular graphics: SHELXL97/PC; software used to prepare material for publication: WinGX.

5-Bromo-2-hydroxybenzophenone (2). 4-Bromophenol (17.3 g, 0.1 mol) was dissolved in absolute diethyl ether (150 mL). The appropriate pyridine (7.9 g, 0.1 mol) was added to the solution, and benzoyl chloride (14.1 g, 0.1 mol) was added to the mixture, which rapidly became hot, and the white solid was precipitated from solution. The precipitate was filtered off and then placed in the flask at 120°C for about 10 min. The flask was then heated to 160°C. Anhydrous aluminum chloride (20 g, 0.15 mol) was added to the flask in portions of about

Table 2

Acetic acid-catalyzed intramolecular rearrangement of di-Schiff base to benzimidazole.[a]

Entry	Substrate	Yield[b] (%)	Product
1	4-Bromo-2-{[2-(4-bromo-benzylidene-amino) phenylimino]phenylmethyl}phenol	87	4-Bromo-2-{α-[1-(4-bromo-phenyl) benzoimidazol-2-yl]-benzyl}phenol
2	4-Bromo-2-{[2-(4-dimethylamino-benzylideneamino) phenylimino]phenylmethyl}phenol	85	4-Bromo-2-{α-[1-(4-dimethylamino-phenyl) benzoimidazol-2-yl]-benzyl}-phenol
3	4-Bromo-2-{[2-(2-thienylamino)-phenylimino]phenylmethyl}phenol	89	4-Bromo-2-{α-[1-(2-thienyl)-benzoimidazol-2-yl]-benzyl}phenol
4	4-Bromo-2-{[2-(2-nitro-benzylidene-amino) phenylimino]phenylmethyl}phenol	79	4-Bromo-2-{α-[1-(2-nitro-phenyl)-benzoimidazol-2-yl]-benzyl}phenol

[a] Reaction conditions: di-Schiff base (0.1 mmol), acetic acid (0.5 mmol), and heated at refluxing.
[b] Isolated yield.

10 g, which rapidly became hot, evolving fumes of HCl. After 2 h, the flask was allowed to cool to room temperature. Hydrochloric acid (5%, 150 mL) was then poured into the flask and was allowed to stand for 24 h. The hydrochloric acid was then decanted from the flask. The yellow solid was washed twice with water and then recrystallized from hot ethanol to give compound **2** as yellow crystals in 47.5% yield. Mp 77–79°C. IR (KBr, cm^{-1}) ν: 3430 (OH), 1626 (C=O), 832, 768, 699. ^{1}H-NMR($CDCl_3$, 500 MHz) δ: 6.95–6.97 (d, 1H, CH=CBr), 7.49–7.67 (m, 7H, Ar-H), 11.91 (s, 1H, Ar-OH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 110.21, 120.31, 120.43, 128.55, 129.10, 132.37, 135.33, 137.10, 138.90, 162.07, 200.46 (C=O). Anal. calcd for $C_{13}H_9BrO_2$: C 56.35, H 3.27, Br 28.83; found: C 56.30, H 3.26, Br 28.84. HRMS calcd for $C_{13}H_{10}BrO_2$ ($M+H^+$): 278.12; found: 278.10.

2-[(2-Aminophenylimino)phenylmethyl]-4-bromophenol (3). 5-Bromo-2-hydroxybenzophenone (27.7 g, 0.1 mol), 1,2-diaminobenzene (10.8 g, 0.1 mol), piperidine (10.2 g, 0.12 mol), and triethylorthoformate (20 mL) were refluxed in absolute ethanol (120 mL) until the red-orange crystalline product started to precipitate from solution. The solution was allowed to cool to room temperature, and the product was collected by filtration and then washed twice with hot ethanol to give compound **3** as red-orange crystals in 65.1% yield. Mp 193–195°C. IR (KBr, cm^{-1}) ν: 3460 (OH), 3367 (NH), 1623 (C=N), 829, 743, 704; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 6.23–7.43 (m, 12H, Ar-H), 14.470 (s, 1H, Ar-OH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 109.71, 115.47, 118.30, 119.86, 121.45, 121.80, 126.09, 128.25 (d), 128.42 (d), 129.51, 133.39, 133.50, 134.13, 135.89, 138.84, 161.39, 174.05 (N=C). Anal. calcd for $C_{19}H_{15}BrN_2O$: C 62.14, H 4.12, Br 21.76, N 7.63; found: C 62.12, H 4.13, Br 21.75, N 7.64. HRMS calcd for $C_{19}H_{15}BrN_2O$ ($M+H^+$): 368.23; found: 368.29. Crystal data for **3**: $C_{19}H_{15}BrN_2O$, Mr = 367.23, crystal system = triclinic, space group = P^{-1}, Z = 2, a = 8.4504 (17) Å, b = 9.4206 (19) Å, c = 11.141 (2) Å, α = 68.94 (3)°, β = 85.40 (3)°, γ = 78.31 (3)°, V = 810.5 (3) Å^3, D = 1.505 mg cm^{-3}, μ = 2.54 mm^{-1}, reflections measured = 3365, independent reflections = 2785, reflections with $I > 2\sigma(I)$ = 2094, with R_{int} = 0.018, T = 295 (2) K, $R[F^2 > 2ó(F^2)]$ = 0.038, $wR(F^2)$ = 0.099, S = 1.03.

General procedure for the preparation of the compounds (4) and (5). To a solution of 2-[(2-aminophenylimino)phenylmethyl]-4-bromophenol (36.7 g, 0.10 mol) in ethanol (120 mL), corresponding aldehyde (0.10 mmol) was added and reacted based on the three conditions as follows: (A) piperidine (10.2 g, 0.12 mol) and triethylorthoformate (12 mL), and the mixture was heated at refluxing; (B) acetic acid (30 g, 0.5 mmol), and it reacted at room temperature in ethanol; (C) acetic acid (30 g, 0.5 mmol), and it was heated at refluxing. The precipitated solid was collected by filtration and washed twice with hot ethanol.

4-Bromo-2-{[2-(2-hydroxybenzylideneamino)phenylimino]-phenylmethyl}-phenol(4c). Yellow solid. Mp 228–230°C. IR (KBr, cm^{-1}) ν: 3429 (OH), 1595 (C=N); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 6.82–7.60 (m, 17H, Ar-H), 8.40 (s, 1H, N=CH), 12.98 (s, 1H, Ar-OH). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 109.56, 117.42, 118.29, 118.95, 119.20, 120.14, 120.92, 122.96, 125.79, 126.97, 128.08, 128.26, 129.28, 132.79, 133.28, 133.69, 134.18, 136.06, 139.74, 141.32, 161.13, 161.67, 162.46, 173.68 (N=C). Anal. calcd for $C_{26}H_{19}BrN_2O_2$: C 66.25, H 4.06, Br 16.95, N 5.94; found: C 66.23, H 4.02, Br 16.98, N 5.97. HRMS calcd for $C_{26}H_{20}BrN_2O_2$ ($M+H^+$): 472.34; found: 472.31. Crystal data for **4c**: $C_{26}H_{19}BrN_2O_2$, Mr = 471.34, crystal system = triclinic, space group = P^{-1}, Z = 2, a = 9.1682 (18) Å, b = 9.7011 (19) Å, c = 12.986 (3) Å, α = 90.87 (3)°, β = 108.79 (3)°, γ = 90.09 (3)°, V = 1089 (4) Å^3, D = 1.436 mg cm^{-3}, μ = 1.91 mm^{-1}, reflections measured = 5132, independent reflections = 4348, reflections with $I > 2\sigma(I)$ = 3028, with R_{int} = 0.018, T = 295 (2) K, $R[F^2 > 2ó(F^2)]$ = 0.034, $wR(F^2)$ = 0.091, S = 1.03.

4-Bromo-2-{[2-(4-benzyloxy-3-methoxy-benzylideneamino)-phenylimino]phenylmethyl}phenol (4f). Yellow solid. Mp 176–178°C. IR (KBr, cm^{-1}) ν: 3429 (OH), 1695 (C=N), 1240 (C—O); ^{1}H-NMR($CDCl_3$, 500 MHz) δ: 3.95 (s, 3H, OCH_3), 5.24 (s, 2H, CH_2), 6.66–7.75 (m, 20H, Ar-H), 8.16 (s, 1H, N=C—H), 14.99 (s, 1H, Ar-OH). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ: 56.01, 70.87, 109.30, 109.62, 112.73, 118.32, 120.00, 121.59, 122.44, 124.25, 125.65, 126.21, 127.27, 128.07, 128.34, 128.38, 128.56, 128.71, 129.30, 130.15, 133.99, 134.12, 135.69, 136.64, 140.24, 144.00, 150.10, 151.10, 159.01, 162.07, 171.51 (N=C). Anal. calcd for $C_{34}H_{27}BrN_2O_3$: C 69.04, H 4.60, Br 13.51, N 4.74; found: C 69.05, H 4.64, Br 13.52, N 4.71. HRMS calcd for $C_{34}H_{28}BrN_2O_3$ ($M+H^+$): 592.49; found: 592.44.

4-Bromo-2-{α-[1-(2-thienyl)benzoimidazol-2-yl]-benzyl}phenol (5g). Orange solid. Mp 243–244°C; IR (KBr, cm^{-1}) ν: 3426 (OH), 1510 (C=N), 1442, 1420, 1370 (thiophene), 1297 (C—N); ^{1}H-NMR (d_6-DMSO, 500 MHz) δ: 6.67–7.82 (m, 16H, Ar-H, N—CH, and thiophene), 10.22 (s, 1H, Ar-OH); ^{13}C-NMR (d_6-DMSO 125 MHz) δ: 59.26 (), 110.28, 112.62, 118.09, 119.94, 122.59, 123.13, 127.74, 128.00, 128.57, 129.57, 130.28, 131.39, 132.72, 132.82, 135.79, 137.82, 143.33, 149.02, 155.33 (N=C). Anal. calcd for $C_{24}H_{17}BrN_2OS$: C 62.48, H 3.71, Br 17.32, N 6.07, S 6.95; found: C 62.45, H 3.70, Br 17.30, N 6.09, S 6.91, HRMS calcd for $C_{24}H_{18}BrN_2OS$ ($M+H^+$): 461.37; found: 461.43. Crystal data for **5g**: $C_{24}H_{17}BrN_2OS$, Mr = 461.37, crystal system = monoclinic, space group = $P2_1/c$, Z = 4, a = 13.623 (3), b = 9.6472 (19), c = 16.962 (3) Å, α = 90.00°, β = 111.98 (3)°, γ = 90.00°, V = 2067.2 (8) Å^3, D = 1.482 mg cm^{-3}, μ = 2.11 mm^{-1}, reflections measured = 9403, independent reflections = 4334, reflections with $I > 2\sigma(I)$ = 2709, with R_{int} = 0.033, T = 295 (2) K, $R[F^2 > 2ó(F^2)]$ = 0.042, $wR(F^2)$ = 0.112, S = 1.02.

SUPPLEMENTARY MATERIAL

Crystallographic data for the structure analysis of the compounds have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 657790 **3**, 672869 **4c**, 651531 **5g**. Copies of these information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (http://www.ccdc.cam.ac.uk).

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