Synthesis of 2,3-Bis(arylamino)benzofurans and 2,3-Bis(arylimino)-2,3-dihydrobenzofurans by a Lewis Acid Catalyzed Reaction of 2-Aryliminophenols with Aryl Isocyanides

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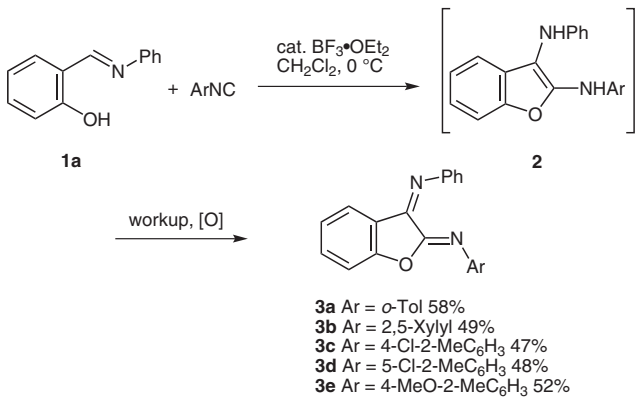
Abstract: An efficient method for the preparation of 2,3-bis(arylamino)benzofurans and 2,3-bis(arylimino)-2,3-dihydrobenzofurans is described that is based on the reaction of 2-aryliminophenols with aryl isocyanides in the presence of a catalytic amount of boron trifluoride diethyl etherate. The reaction gives 2,3-bis(arylamino)benzofurans, some of which are transformed into 2,3-bis(arylimino)-2,3-dihydrobenzofurans by air oxidation, mostly during workup.

Key words: benzofurans, *o*-hydroxybenzylideneamines, isocyanides, boron trifluoride, imidoyl cations

Because some molecules containing a benzofuran moiety are known to display a variety of biological activities,[1] the development of new, efficient methods for the synthesis of benzofurans continues to be of interest.[2] In this paper we report a facile preparation of 2,3-diaminobenzofuran derivatives, 2,3-bis(arylimino)-2,3-dihydrobenzofurans and 2,3-bis(arylamino)benzofurans, by a Lewis acid catalyzed reaction of readily available 2-aryliminophenols with aryl isocyanides. There have been only a few reports on the synthesis of these types of benzofuran derivatives.[3] A synthesis of 2,3-bis(arylimino)-2,3-dihydrophenanthro[9,10-*b*]furans has been achieved by successive treatment of RCOC(=N_2)COR (RR=2,2′-biphenylene) with Ph_3P=NAr^1 and Ar^2NC.[3a] 2-Alkyl(or phenyl)amino-3-(2-hydroxybenzylideneamino)benzofurans have been prepared in lower yields under the conditions of the Ugi four-component (isocyanides, ammonium formate and two equivalents of 2-hydroxybenzaldehydes) condensation.[3b]

2-(Phenylimino)phenol (**1a**), which is available from 2-hydroxybenzaldehyde and aniline, was chosen as the first substrate and allowed to react with several aromatic isocyanides in dichloromethane at 0 °C in the presence of a catalytic amount of a Lewis acid. We chose boron trifluoride diethyl etherate as a Lewis acid because we have previously had much success in heterocycle syntheses using this Lewis acid in catalyzed reactions utilizing isocyanides.[4] As expected, the reactions proceeded smoothly and cleanly. After usual workup followed by purification of the crude products by column chromatography on silica gel, 2,3-bis(arylimino)-2,3-dihydrobenzofurans **3** were obtained in moderate yields; the moderate yields were probably caused by oxidation of the initially formed 2,3-bis(arylamino)benzofurans **2** during workup, as illustrated in Scheme 1. Although the stereochemistries of the 2- and 3-imino moieties of the products **3** could not be confirmed spectroscopically, we tentatively assigned them as 2-(*Z*) and 3-(*Z*) because these conformations give the least sterically crowded structures. We were unable to prepare the corresponding 2,3-diimino-2,3-dihydrobrnzofuran derivative using *tert*-butyl isocyanide in place of aryl isocyanides; in this case, progress of the reaction was extremely sluggish and the starting material **1a** was recovered almost quantitatively after overnight reaction at room temperature. One of the reasons for this may be ascribed to the steric bulk of this isocyanide.



Scheme 1 Preparation of 2,3-diimino-2,3-dihydrobenzofurans

Next, 2-[4-chlorophenylimino]phenol (**1b**), which is available by condensation of 2-hydroxybenzaldehyde with 4-chlorobenzeneamine, was treated with 1-isocyano-4-methoxy-2-methylbenzene according to the procedure described above. The reaction gave a mixture of the corresponding 2,3-diaminobenzofuran derivative **2f** and 2,3-diimino-2,3-dihydrobenzofuran derivative **3f**, as judged by ^{1}H NMR of the crude material after workup. Standing a solution of this mixture in hexane–diethyl ether (1:1) in air overnight at room temperature effected the oxidation of **2f** to **3f**, and enabled the isolation of **3f** in pure form (53%) by simply collecting the precipitate that appeared in the solution (Scheme 2).

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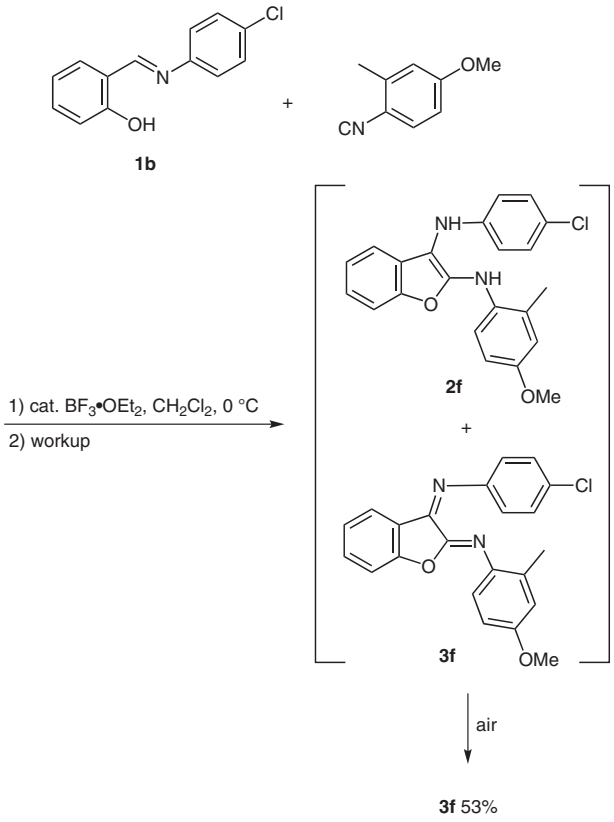
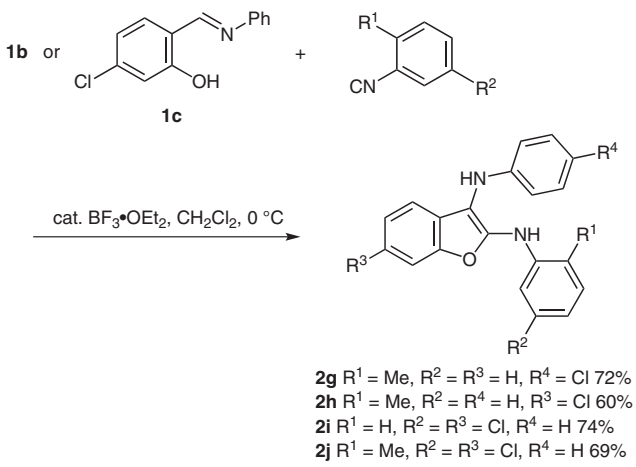


Scheme 2 Formation of a 2,3-diamino-2,3-dihydrobenzofuran

A similar Lewis acid catalyzed reaction of **1b** with 1-isocyano-2-methylbenzene followed by workup and purification by column chromatography on silica gel, however, provided the corresponding 2,3-diaminobenzofuran derivative **2g**, in a fair yield; this compound was found to be considerably more stable toward oxidation. Subsequently, the reaction of 5-chloro-2-phenyliminophenol (**1c**), which is accessible by condensation of 4-chloro-2-hydroxybenzaldehyde with aniline, with aryl isocyanides, proved to give similar results. Thus, treatment of **1c** with aryl isocyanides in a manner similar to that described above gave the corresponding 2,3-bis(arylamino)benzofurans **2h**–**j**, as outlined in Scheme 3. Yields for the preparation of these products, which are also summarized in Scheme 3, are generally fair-to-good.

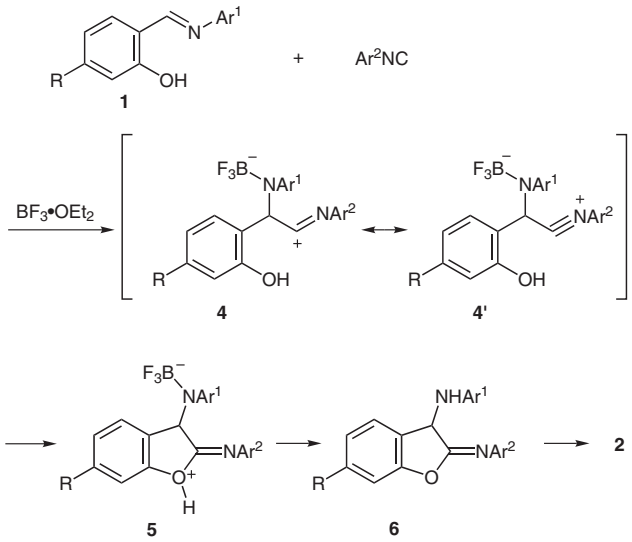
It should be noted that the attempted reactions of 2-(*tert*-butylimino)phenol, 2-(4-methoxyphenylimno)phenol, and 5-methoxy-2-phenyliminophenol with 1-isocyano-2-methylbenzene under conditions similar to those mentioned above, only resulted in almost quantitative recovery of the starting material in each case, i.e. no reactions occurred. Elevating the reaction temperature to reflux resulted in the formation of intractable mixtures of products. The methoxy substituent is thought to decrease the reactivity of these substrates in the present Lewis acid reaction due to its electron-donating property.

A probable pathway to 2,3-diaminobenzofurans **2** is depicted in Scheme 4. Thus, the isocyano-carbon of an aryl isocyanide attacks the imino-carbon of the 2-arylimino-



Scheme 3 preparation of 2,3-diaminobenzofurans

phenol **1**, which is activated by boron trifluoride, to generate an imidoyl cation intermediate **4**. This cation center is trapped through intramolecular attack of the hydroxy oxygen to give an oxonium ion intermediate **5**. Deprotonation and removal of boron trifluoride gives 3-arylamino-2-arylimino-2,3-dihydrobenzofuran **6**, which then tautomerizes to **2**. The results described above imply that: (1) the oxidation of **2** to **3** is inhibited by substitution of a chloro group on the benzene rings of 2-(arylimino)phenols **1**; (2) the substitution of a methoxy group on the 4-position of isocyanides facilitates the oxidation.



Scheme 4 A probalble pathway to the products

In summary, the synthesis of 2,3-bis(arylimino)-2,3-dihydrobenzofurans and 2,3-bis(arylamino)benzofurans, based on the reaction of 2-aryliminophenols with aryl isocyanides catalyzed by a Lewis acid, has been achieved. The present procedure can serve as the first practical method for the synthesis of 2,3-diaminobenzofuran derivatives. The ready availability of the starting materials and the simplicity of the operations make the present method attractive.

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra were measured with a JEOL JMS AX505 HA spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. Isocyanides were prepared by our previously reported procedure.[5] 2-Aryliminophenols **1b**[6] and **1c**[7] were prepared by treating the required 2-hydroxybenzaldehyde with the corresponding arylamine. All other chemicals used in this study are commercially available.

2-(2-Methylphenylimino)-3-phenylimino-2,3-dihydrobenzofuran (3a); Typical Procedure

To a stirred solution of **1a** (0.20 g, 1.0 mmol) and freshly distilled 1-isocyano-2-methylbenzene (0.18 g, 1.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C, was added freshly distilled $BF_3{\cdot}OEt_2$ (14 mg, 0.10 mmol). After stirring for 1.5 h at the same temperature, the mixture was diluted with CH_2Cl_2 (10 mL) and sat. aq $NaHCO_3$ (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated and the residue was subjected to column chromatography on silica gel (Et_2O–hexane, 1:9) to afford **3a**.

Yield: 0.18 g (58%); orange solid; mp 81–83 °C (hexane–CH_2Cl_2).

IR (KBr): 1645, 1607 cm^{-1}.

^{1}H NMR: δ = 2.35 (s, 3 H), 6.73 (d, *J* = 7.3 Hz, 1 H), 6.87 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.08–7.14 (m, 4 H), 7.19–7.28 (m, 4 H), 7.41 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.46 (dd, *J* = 7.8, 7.3 Hz, 2 H).

^{13}C NMR: δ = 18.25, 112.36, 118.09, 118.23, 121.25, 123.44, 125.08, 125.14, 126.00, 126.05, 128.68, 129.43, 130.37, 134.82, 144.11, 149.80, 150.62, 153.58, 160.67.

MS (EI, 70 eV): *m*/*z* (%) = 312 (18) [M]$^+$, 297 (100).

Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.61; H, 5.28; N, 8.94.

2-(2,5-Dimethylphenylimino)-3-phenylimino-2,3-dihydrobenzofuran (3b)

Orange viscous oil; R_f = 0.36 (THF–pentane, 1:19).

IR (neat): 1640, 1607 cm^{-1}.

^{1}H NMR: δ = 2.29 (s, 3 H), 2.36 (s, 3 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 6.86 (dd, *J* = 7.8, 7.3 Hz, 1 H), 6.94 (d, *J* = 7.8 Hz, 1 H), 7.00 (s, 1 H), 7.08–7.11 (m, 3 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 7.25 (t, *J* = 7.3 Hz, 1 H), 7.41 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.45 (dd, *J* = 7.8, 7.3 Hz, 2 H).

^{13}C NMR: δ = 17.77, 21.07, 112.40, 118.11, 118.23, 121.64, 123.39, 125.05, 125.90, 126.03, 128.64, 129.43, 130.17, 134.79, 135.58, 143.98, 149.67, 150.64, 153.58, 160.70.

MS (EI, 70 eV): *m*/*z* (%) = 326 (23) [M]$^+$, 311 (100).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.80; H, 5.61; N, 8.66.

2-(4-Chloro-2-methylphenylimino)-3-phenylimino-2,3-dihydrobenzofuran (3c)

Orange needles; mp 123–127 °C (hexane–CH_2Cl_2).

IR (KBr): 1640, 1607 cm^{-1}.

^{1}H NMR: δ = 2.33 (s, 3 H), 6.74 (d, *J* = 7.3 Hz, 1 H), 6.88 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.07–7.11 (m, 3 H), 7.15 (d, *J* = 8.2 Hz, 1 H), 7.21 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.26 (t, *J* = 7.3 Hz, 1 H), 7.42–7.47 (m, 4 H).

^{13}C NMR: δ = 18.19, 112.31, 118.01, 118.20, 122.68, 123.64, 125.21, 126.08, 126.11, 128.74, 129.47, 130.24, 132.72, 134.92, 142.55, 150.23, 150.49, 153.44, 160.5.

MS (EI, 70 eV): *m*/*z* (%) = 346 (30) [M]$^+$, 331 (100).

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.60; H, 4.51; N, 8.01.

2-(5-Chloro-2-methylphenylimino)-3-phenylimino-2,3-dihydrobenzofuran (3d)

Orange viscous oil; R_f = 0.32 (THF–hexane, 1:4).

IR (neat): 1645, 1607 cm^{-1}.

^{1}H NMR: δ = 2.30 (s, 3 H), 6.75 (d, *J* = 7.8 Hz, 1 H), 6.89 (t, *J* = 7.8 Hz, 1 H), 7.08–7.10 (m, 3 H), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.18 (d, *J* = 8.2 Hz, 1 H), 7.20 (d, *J* = 1.8 Hz, 1 H), 7.27 (t, *J* = 7.3 Hz, 1 H), 7.41–7.47 (m, 3 H).

^{13}C NMR: δ = 17.76, 112.43, 118.00, 118.20, 121.26, 123.70, 125.04, 125.26, 126.08, 129.05, 129.49, 131.25, 131.35, 134.98, 145.09, 150.45, 150.48, 153.40, 160.54.

MS (EI, 70 eV): *m*/*z* (%) = 346 (29) [M]$^+$, 331 (100).

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.53; H, 4.57; N, 7.83.

2-(4-Methoxy-2-methylphenylimino)-3-phenylimino-2,3-dihydrobenzofuran (3e)

Orange needles; mp 153–157 °C (hexane–CH_2Cl_2).

IR (KBr): 1634, 1607 cm^{-1}.

^{1}H NMR: δ = 2.41 (s, 3 H), 3.983 (s, 3 H), 6.69 (dd, *J* = 7.8, 1.4 Hz, 1 H), 6.79–6.87 (m, 3 H), 7.07 (d, *J* = 7.8 Hz, 2 H), 7.12 (d, *J* = 7.8 Hz, 1 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.41 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.44 (dd, *J* = 7.8, 7.3 Hz, 2 H).

^{13}C NMR: δ = 18.76, 55.32, 111.31, 112.29, 115.65, 118.16, 118.29, 123.28, 123.48, 124.91, 126.17, 128.84, 129.42, 134.63, 136.62, 148.85, 150.89, 153.87, 157.50, 160.67.

MS (EI, 70 eV): *m*/*z* (%) = 342 (24) [M]$^+$, 327 (100).

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.16; H, 5.29; N, 8.00.

3-(4-Chlorophenyl)imino-2-(4-methoxy-2-methylphenylimino)-2,3-dihydrobenzofuran (3f)

A solution of **1b** (0.23 g, 1.0 mmol) and freshly distilled 1-isocyano-4-methoxy-2-methylbenzene (0.22 g, 1.5 mmol) in CH_2Cl_2 (3 mL) was treated with a catalytic amount of $BF_3{\cdot}OEt_2$ in a manner similar to that described in the typical procedure. After workup, the residue was dissolved in Et_2O–hexane (1:2, 20 mL), the solution was allowed to stand in air overnight and the precipitated **3f** was collected.

Yield: 0.20 g (53%); orange needles; mp 204–208 °C (hexane–CH_2Cl_2).

IR (KBr): 1638, 1601 cm^{-1}.

^{1}H NMR: δ = 2.40 (s, 3 H), 3.83 (s, 3 H), 6.79–6.82 (m, 3 H), 6.91 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.03 (d, *J* = 8.7 Hz, 2 H), 7.14 (d, *J* = 8.2 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.44 (dd, *J* = 7.8, 7.3 Hz, 1 H).

^{13}C NMR: δ = 18.76, 55.33, 111.38, 112.48, 115.69, 119.72, 119.94, 123.42, 123.59, 125.97, 129.61, 130.32, 134.58, 135.01, 136.43, 148.58, 149.25, 154.33, 157.68, 160.82.

MS (EI, 70 eV): *m/z* (%) = 376 (25) $[M]^+$, 361 (100).

Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.07; H, 4.54; N, 7.25.

3-(4-Chlorophenyl)amino-2-(2-methylphenylamino)benzofuran (2g)

Yellow viscous oil: R_f = 0.18 (CH_2Cl_2–hexane,1:4).

IR (neat): 3391, 1651, 1603 cm^{-1}.

^1H NMR: δ = 2.10 (s, 3 H), 4.80 (br s, 1 H), 5.74 (br s, 1 H), 6.60 (d, *J* = 7.3 Hz, 2 H), 6.73 (t, *J* = 7.3 Hz, 1 H), 6.84 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.01 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.04–7.14 (m, 6 H), 7.19 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR: δ = 17.50, 102.45, 111.74, 113.88, 116.83, 117.22, 119.19, 122.06, 122.16, 125.58, 127.06, 128.70, 129.00, 129.45, 130.74, 138.93, 145.57, 147.80, 149.57.

MS (CI): *m/z* (%) = 349 (100) $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{17}ClN_2O$: C, 72.31; H, 4.91; N, 8.03. Found: C, 72.26; H, 5.07; N, 8.04.

6-Chloro-2-(2-methylphenyl)amino-3-phenylaminobenzofuran (2h)

Yellow viscous oil: R_f = 0.25 (CH_2Cl_2–hexane, 1:4).

IR (neat): 3391, 1651, 1603 cm^{-1}.

^1H NMR: δ = 2.10 (s, 3 H), 4.80 (s, 1 H), 5.74 (s, 1 H), 6.60 (d, *J* = 7.3 Hz, 2 H), 6.73 (t, *J* = 7.3 Hz, 1 H), 6.84 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.02 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.05 (d, *J* = 7.3 Hz, 1 H), 7.08–7.14 (m, 5 H), 7.19 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR: δ = 17.50, 102.45, 111.74, 113.88, 116.83, 117.22, 119.19, 122.06, 122.16, 125.18, 127.06, 128.70, 129.00, 129.45, 130.74, 138.93, 145.57, 147.80, 149.57.

MS (CI): *m/z* (%) = 349 (100) $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{17}ClN_2O$: C, 72.31; H, 4.91; N, 8.03. Found: C, 72.26; H, 5.00; N, 7.84.

6-Chloro-2-(3-chlorophenyl)amino-3-phenylaminobenzofuran (2i)

Yellow viscous oil; R_f = 0.20 (Et_2O–hexane, 1:4).

IR (neat): 3391, 1651, 1601 cm^{-1}.

^1H NMR: δ = 4.91 (s, 1 H), 6.16 (s, 1 H), 6.68 (d, *J* = 7.8 Hz, 2 H), 6.83 (t, *J* = 7.3 Hz, 1 H), 6.91 (ddd, *J* = 7.8, 7.3, 1.8 Hz, 2 H), 7.09 (dd, *J* = 2.3, 1.8 Hz, 1 H), 7.13–7.21 (m, 5 H), 7.32 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR: δ = 102.95, 111.95, 113.86, 114.46, 116.25, 117.49, 119.40, 121.59, 122.54, 128.50, 128.89, 129.52, 130.34, 135.10, 141.89, 145.43, 147.89, 148.46.

MS (CI): *m/z* (%) = 369 (100) $[M + 1]^+$.

Anal. Calcd for $C_{20}H_{14}Cl_2N_2O$: C, 65.06; H, 3.82; N, 7.59. Found: C, 64.81; H, 3.71; N, 7.42.

6-Chloro-2-(5-chloro-2-methylphenyl)amino-3-phenylaminobenzofuran (2j)

Beige solid; mp 124–129 °C (hexane–Et_2O).

IR (KBr): 3397, 1651, 1601 cm^{-1}.

^1H NMR: δ = 2.14 (s, 3 H), 4.94 (s, 1 H), 5.81 (s, 1 H), 6.70 (dd, *J* = 8.7, 0.9 Hz, 2 H), 6.84 (t, *J* = 7.8 Hz, 1 H), 6.86 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.04 (d, *J* = 7.8 Hz, 1 H), 7.16 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.18–7.23 (m, 4 H), 7.34 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR: δ = 17.01, 104.12, 112.04, 114.03, 115.94, 117.60, 119.45, 121.58, 122.73, 123.10, 128.59, 128.85, 129.52, 131.51, 132.56, 140.16, 141.98, 145.23, 148.00.

MS (CI): *m/z* (%) = 383 (100) $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{16}Cl_2N_2O$: C, 65.81; H, 4.21; N, 7.31. Found: C, 65.78; H, 4.38; N, 7.34.

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