Synthesis of Carbazoles from *N*-(*N*,*N*-Diarylamino)phthalimides with Aluminum Chloride via Diarylnitrenium Ions

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Generation of diarylnitrenium ions from *N*-(*N*,*N*-diarylamino)phthalimides by treatment with $AlCl_3$ in benzene or in 1,2-dichloroethane leads to formation of carbazoles by intramolecular C−C bond formation. The reaction proceeds in synthetically useful yields.

Introduction

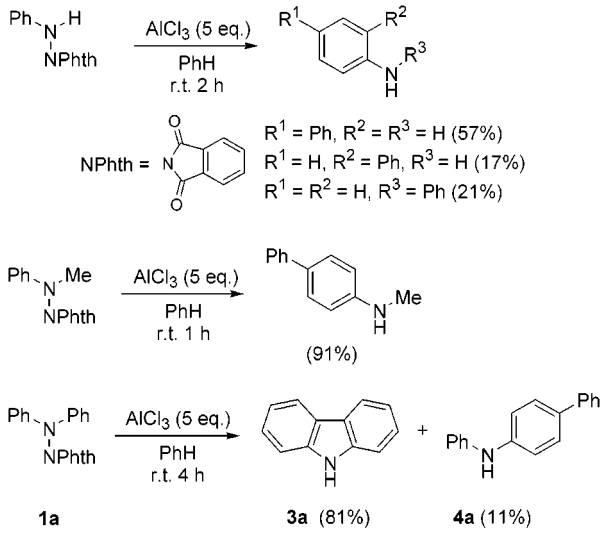
From the extensive work of Gassman and his group, the nitrenium ion has received increasing attention from synthetic, theoretical, and biological perspectives.[1] However, despite the potential utility of the nitrenium ion as an electrophilic nitrogen, its synthetic applications remain limited, mainly because it is a short-lived reaction intermediate.

Previously, we reported that *N*-phenylaminophthalimide reacts with $AlCl_3$ in benzene to generate a phenylnitrenium ion that is trapped by benzene to give *o*- and *p*-aminobiphenyls and *N*-phenylaniline.[2] On the other hand, with *N*-(*N*-methyl-*N*-phenylamino)phthalimide, the cleavage of the N−N bond results in a positive charge exclusively on the para position of the methylamino group, and 4-methylaminobiphenyl was obtained in 91% yield.[3] In an extension of this work, we now have investigated the reaction of *N*-(*N*,*N*-diarylamino)phthalimides (**1**) with $AlCl_3$ in benzene, with the expectation that $AlCl_3$-mediated cleavage of the N−N bond might give a diarylnitrenium ion.[4]

Results and Discussion

Treatment of *N*-(*N*,*N*-diphenylamino)phthalimide (**1a**) with $AlCl_3$ (5 mol equiv) in benzene for 4 h at room temperature gave carbazole (81%) along with *N*-*p*-biphenyl-*N*-phenylamine (11%), which indicates that $AlCl_3$-mediated heterolytic cleavage of the N−N bond produces a diphenylnitrenium ion (**2a**). Intramolecular trapping of canonical forms involving one of the benzene rings by the adjacent ring would produce carbazole (**3a**). In principle, arylation of the phenylnitrenium intermediate could occur at three distinct sites where the positive charge is preferentially located. Attack could occur at nitrogen, at the para ring carbon, or at the ortho ring carbons. In the present case, the ortho ring carbon is attacked intramolecularly by the adjacent ortho ring carbon to form a new C−C bond rather than being attacked intermolecularly by solvent benzene to give *N*-*o*- and -*p*-biphenyl-*N*-phenylamines.

Scheme 1



Two reports of generation of a diarylnitrenium ion have hitherto appeared. In one, photolysis of *N*-(diphenylamino)-2,4,6-trimethylpyridinium tetrafluoroborate[5] gave diphenylamine (10%) and carbazole (3%) in low yields. In a second report, decomposition of 1,1-diphenylhydrazine with trifluoromethanesulfonic acid in benzene[6] produced only *N*-*p*-biphenyl-*N*-phenylamine (89%).

To develop a synthetically more useful carbazole synthesis, we investigated the production of **3** with different Lewis acids ($AlCl_3$, $TiCl_4$, and $BF_3{\cdot}OEt_2$). We found that $AlCl_3$-mediated decomposition of **1** gives the best results. With other Lewis acids, a large amount of unreacted starting material remained under comparable reaction conditions. For example, treatment of **1a** with $BF_3{\cdot}OEt_2$ (10 mol equiv) in benzene for 24 h at room temperature afforded recovery of **1a** in 92% yield. Various solvents such as benzene, toluene, 1,3,5-trimethylbenzene, penta- and hexafluorobenzenes, chlorobenzene, 1,2-dichloroethane, carbon disulfide, and tetrahydrofuran

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Scheme 2

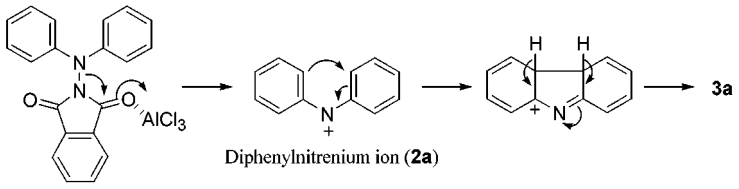
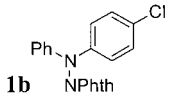
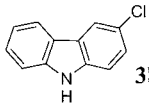
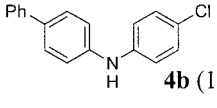
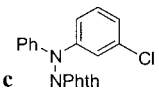
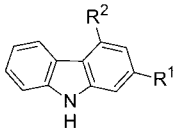
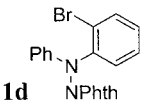
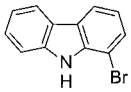
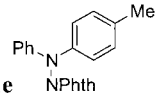
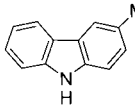
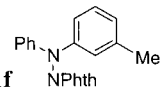
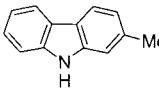
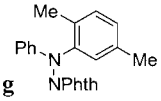
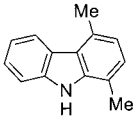
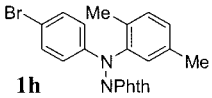
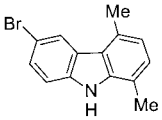
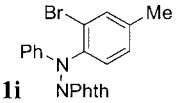
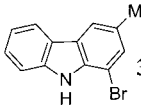


Table 1. Reaction of *N*-(*N*,*N*-Diarylamino)phthalimides with $AlCl_3$

entry	starting material	method[a]	time (h)	product (%)
1	Ph_2N-NPhth (**1a**)	A	4	carbazole (**3a**) (81) Ph-NH-Ph-*p*-Ph (**4a**) (11)
2	**1a**	B	0.5	**3a** (80)
3	 **1b**	A	6	 **3b** (33)  **4b** (12)
4	**1b**	B	1	**3b** (50)
5	 **1c**	A	4	 **3c** (64): (R^1 = Cl, R^2 = H) **4c** (15): (R^1 = H, R^2 = Cl)
6	**1c**	B	4	**3c** (40) **4c** (17)
7	 **1d**	A	17	 **3d** (73)
8	 **1e**	A	1	 **3e** (14)
9	**1e**	B	0.5	**3e** (81)
10	 **1f**	A	4	 **3f** (81)
11	 **1g**	A	1	 **3g** (89)
12	 **1h**	A	4	 **3h** (39) **3g** (14)
13	 **1i**	A	2	 **3i** (22) **8** (43) **9** (4)
14	**1i**	C	1	**3i** (52)

[a] For methods A, B, and C (see Experimental Section).

also were examined. Among these, benzene proved to be the solvent of choice despite formation of phenylated byproducts. 1,2-Dichloroethane is also suitable in some cases. As for the examination of leaving groups from the diarylamine moiety, we have synthesized N-amino, N-benzoyl, and N-succinoyl derivatives (**5**, **6**, and **7**, respectively) in addition to phthalimide derivatives (**1**). From **6**, the reaction did not proceed at all and starting compound (**6**) was recovered in 91% yield. From **5**, **7**, and **1a**, carbazole was obtained in yields of 33%, 57%, and 81%, respectively. From this result, it is clear that the phthalimido group plays an important role for the generation and stabilization of a diarylnitrenium ion. This allows formation of carbazole in good yield by intramolecular cyclization. Several carbazoles (**3**) were obtained in this way. The results are presented in Table 1.

In the case of **1e** and **1i**, which have a methyl group substituted at the para position to nitrogen, some adjustments to the reaction procedure were necessary to obtain

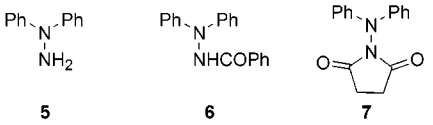


Figure 1.

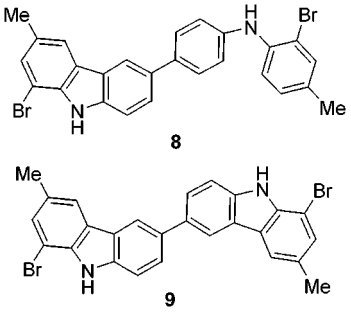


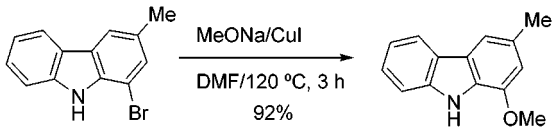
Figure 2.

products in acceptable yields. According to method A, the color of the reaction mixture containing **1e** quickly turned from brown to black and considerable amounts of tarry products were obtained. The yield of **3e** was improved very much by slow addition of **1e** in 1,2-dichloroethane to $AlCl_3$ in 1,2-dichloroethane (entry 9). On the other hand, using this procedure, we obtained **3i** again in low yield from **1i** (entry 13). Careful isolation of the other products of this reaction indicated the presence of **8** and trace amounts of the dimeric product (**9**). The use of a dilution method (method C) improved the yield of **3i** somewhat (52%, entry 14). Generally, the method that has been most utilized for the preparation of aromatic carbazoles from noncarbazole precursors is the dehydrogenation of 1,2,3,4-tetrahydrocarbazoles.[7] The Fischer cyclization reaction can afford 1,2,3,4-tetrahydrocarbazoles. However, the cyclization of the 2,5-dimethyl phenylhydrazone of cyclohexanone yielded a mixture of 1,2-, 1,4-, and 2,4-dimethylcarbazoles as the results of methyl migration prior to dehydrogenation.[8] Using the present method, we obtained 1,4-dimethylcarbazole (**3g**) in 89% yield from **1g** and no methyl migration was observed (entry 11).

Synthesis of Murrayafoline A. In the case of methoxy-substituted **1**, the reaction did not proceed smoothly and production of many compounds was observed by TLC analysis. For the synthesis of methoxycarbazoles, the corresponding bromocarbazoles are synthesized by the present method, and the replacement of the bromine atom with a methoxy group was carried out by the reported method.[9]

We applied this strategy to the synthesis of a carbazole alkaloid, 1-methoxy-3-methyl-9*H*-carbazole (murrayafoline A) (**10**), using the same methodology described above. This member of the 1-oxygenated C_{13}-carbazole class of alkaloids has been synthesized by several methods.[10] We achieved the synthesis of **10** in 92% yield by direct methoxide displacement of bromine from 1-bromo-3-methyl-9*H*-carbazole (**3i**). The present procedure by

Scheme 3



which a methoxy group can be introduced at the final stage of manipulation of reactions will be potentially useful for the synthesis of other methoxycarbazole derivatives, depending on the availability of the corresponding bromo compound.[11]

In conclusion, diarylnitrenium ions were generated from *N*-(*N*,*N*-diarylamino)phthalimides with $AlCl_3$ and carbazoles were obtained by intramolecular C−C bond formation.

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were recorded at 270 MHz (^{1}H) and 125 MHz (^{13}C) in $CDCl_3$ with TMS as the internal reference. Mass spectra were measured with direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this university. All purchased reagents were of reagent-grade quality and were used without further purification.

Materials. The synthesis of starting materials (**1a**−**g**) were reported previously,[12] and **1i** was prepared according to the same procedure.[12] Compound **1h** was prepared from *N*-(4-bromophenyl)-*N*-(2,5-dimethylphenyl)amine (**11**) by N-nitrosation, subsequent reduction, and finally phthaloylation[2] according to the published procedure.[13] Compound **11** was obtained by Ullmann[14] reaction of *N*-(2,5-dimethylphenyl)-acetamide with 1,4-dibromobenzene followed by hydrolysis of the acetamido group according to the same literature method.[13]

***N*-[*N*-(4-Bromophenyl)-*N*-(2,5-dimethylphenyl)amino]-phthalimide (1h).** A pale yellow solid: mp 148 °C (petroleum ether); IR (KBr) 1790, 1740, 1590, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.36 (s, 3H), 6.43 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.39 (s, 1H), 7.77−7.85 (m, 2H), 7.88−7.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.88, 20.91, 112.53, 114.95, 123.89, 128.04, 129.05, 129.60, 131.26, 132.09, 133.87, 134.84, 137.50, 140.81, 144.89, 166.30; EI-MS *m*/*z* 422 (M^+ + 2, 75.5), 420 (M^+, 74.4), 194 (100). Anal. Calcd for $C_{22}H_{17}N_2O_2Br$: C, 62.72; H, 4.07; N, 6.65. Found: C, 62.71; H, 4.14; N, 6.69.

***N*-[*N*-(2-Bromo-4-methylphenyl)-*N*-phenylamino]-phthalimide (1i).** Pale yellow crystals: mp 246−248 °C (CH_2Cl_2); IR (KBr) 1800, 1740, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 6.69 (d, J = 8.1 Hz, 2H), 6.93 (t, J = 7.3 Hz, 1H), 7.13 (dd, J = 8.1, 1.8 Hz, 1H), 7.22 (t, J = 7.9 Hz, 2H), 7.48 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.76−7.84 (m, 2H), 7.86−7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.67, 114.96, 121.58, 121.83, 123.83, 128.93, 129.19, 129.44, 129.63, 134.49, 134.75, 138.92, 139.51, 145.07, 166.02; EI-MS *m*/*z* 408 (M^+ + 2, 91.1), 406 (M^+, 91.2), 327 (27.6), 180 (100). Anal. Calcd for $C_{21}H_{15}N_2O_2Br$: C, 61.93; H, 3.71; N, 6.88. Found: C, 61.88; H, 3.86; N, 6.85.

The carbazoles (**3a**−**g**, **4c)** and **4a** are known compounds, and their physical constants and spectral data are in agreement with the literature data. **9*H*-Carbazole (3a)**: mp 240−243 °C (lit.[15] 245 °C). **3-Chloro-9*H*-carbazole (3b)**: mp 202−

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(15) Zelinsky, N. D.; Titz, I.; Gaverdowskaja, M. *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 2590.

205 °C (lit.[16] 198−199 °C). **2-Chloro-9*H*-carbazole (3c)**: mp 242−244 °C (lit.[17] 241 °C). **4-Chloro-9*H*-carbazole (4c)**: mp 94−95 °C (lit.[17] 95 °C). **1-Bromo-9*H*-carbazole (3d)**: mp 110−111 °C (lit.[18] 111−112 °C). **3-Methyl-9*H*-carbazole (3e)**: mp 204−206 °C (lit.[19] 207−208 °C). **2-Methyl-9*H*-carbazole (3f)**: mp 269−274 °C (lit.[19] 264−266 °C). **1,4-Dimethyl-9*H*-carbazole (3g)**: mp 97−98 °C (lit.[19] 98.2−98.3 °C). ***N*-(Biphenyl-4-yl)-*N*-phenylamine (4a)**: mp 113 °C (lit.[20] 112 °C).

General Procedure: Reaction of *N*-(*N*,*N*-Diarylamino)-phthalimides (1) with $AlCl_3$. Method A. To a solution of **1** (1 mmol) in benzene (10 mL) was added $AlCl_3$ (5 equiv) at room temperature, and the progress of the reaction was monitored by TLC. When TLC indicated the disappearance of starting material, the reaction was quenched with 10% NaOH under ice cooling, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography over silica gel (*n*-hexane/EtOAc = 5:1−2:1) afforded the corresponding products.

Method B. To a mixture of $AlCl_3$ (5 equiv) and 1,2-dichloroethane (10 mL) was added dropwise a solution of **1** (1 mmol) in 1,2-dichloroethane (2 mL) at room temperature, and the progress of the reaction was monitored by TLC. When TLC indicated the disappearance of starting material, the reaction was quenched with 10% NaOH under ice cooling, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography over silica gel (*n*-hexane/EtOAc = 5:1−2:1) afforded the corresponding products.

6-Bromo-1,4-dimethyl-9*H*-carbazole (3h).[21] Colorless crystals: mp 137−138 °C (EtOAc/*n*-hexane); IR (KBr) 3400, 1590, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H), 2.82 (s, 3H), 6.95 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.50 (dd, J = 8.4, 1.8 Hz, 1H), 8.10 (br s, 1H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.50, 20.38, 111.78, 112.12, 117.17, 120.47, 121.21, 125.03, 126.15, 126.82, 127.64, 130.98, 137.89, 139.11; EI-MS *m*/*z* 275 (M^+ + 2, 99.9), 273 (M^+, 100), 260 (16.4), 194 (28.8). Anal. Calcd for $C_{14}H_{12}NBr$: C, 61.33; H, 4.41; N, 5.11. Found: C, 61.54; H, 4.36; N, 4.99.

***N*-(Biphenyl-4-yl)-*N*-(4-chlorophenyl)amine (4b).** White solid: mp 119−120 °C (*n*-hexane); IR (KBr) 3430, 1610, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98−7.18 (m, 4H), 7.19−7.36 (m, 3H), 7.42 (t, J = 7.5 Hz, 2H), 7.48−7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 118.08, 119.05, 125.72, 126.54, 126.71, 128.06, 128.75, 129.32, 134.26, 140.68, 141.59, 142.04; EI-MS *m*/*z* 281 (M^+ + 2, 33.5), 279 (M^+, 100), 243 (11.9). Anal. Calcd for $C_{18}H_{14}NCl$: C, 77.28; H, 5.04; N, 5.01. Found: C, 77.22; H, 5.03; N, 5.01.

***N*-[4-(8-Bromo-6-methyl-9*H*-carbazol-3-yl)phenyl]-*N*-(2-bromo-4-methylphenyl)amine (8).** Colorless crystals: mp 167−168 °C (EtOAc/*n*-hexane); IR (KBr) 3430, 2920, 1610, 1530, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.51 (s, 3H), 5.98 (br s, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.13−7.28 (m, 3H), 7.34−7.42 (m, 2H), 7.48 (d, J = 8.3 Hz, 1H), 7.57−7.68 (m, 3H), 7.83 (s, 1H), 8.14 (s, 1H), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.26, 21.19, 103.70, 111.18, 112.81, 116.87, 118.61, 119.44, 119.49, 124.10, 124.76, 125.59, 128.09, 128.76, 129.21, 130.41, 131.20, 133.02, 133.26, 135.56, 136.80, 138.59, 138.63, 141.09; EI-MS *m*/*z* 522 (M^+ + 2, 51.7), 520 (M^+, 100), 518 (50.5), 260 (10.4). Anal. Calcd for $C_{26}H_{20}N_2Br_2$: C, 60.02; H, 3.87; N, 5.38. Found: C, 59.89; H, 3.82; N, 5.11.

8,8′-Dibromo-6,6′-dimethyl-9*H*,9′*H*-[3,3′]bicarbazoyl (9). White solid: mp 260−268 °C; IR (KBr) 3420, 1570, 1510, 1300 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50 (s, 6H), 7.48 (s, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.85 (dd, J = 8.6, 2.0 Hz, 2H), 8.07 (s, 2H), 8.51 (s, 2H), 11.33 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 20.57, 103.09, 111.80, 118.47, 119.64, 123.09, 124.47, 125.44, 128.79, 129.13, 132.54, 136.76, 139.15; EI-MS *m*/*z* 520 (M^+ + 2, 51.7), 518 (M^+, 100), 516 (50.8), 439 (8.8), 437 (10.6), 357 (8.4), 259 (9.0), 218 (7.3), 179 (12.9); HR-MS (FAB) *m*/*z* for $C_{26}H_{18}N_2Br_2$ calcd 515.9836, found 515.9841.

Reaction of *N*-[*N*-(2-Bromo-4-methylphenyl)-*N*-phenylamino]phthalimide (1i) with $AlCl_3$. Method C. A solution of **1i** (0.600 g, 1.47 mmol) in 1,2-dichloroethane (10 mL) was added dropwise to a mixture of $AlCl_3$ (2.79 g, 22.1 mmol) and 1,2-dichloroethane (700 mL) over 40 min at room temperature. After the mixture was stirred for 20 min, the reaction was quenched with 10% NaOH under ice cooling. The organic layer was washed with brine (2 × 100 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography over silica gel (*n*-hexane/THF = 10:1) afforded **3i** (0.199 g, 52%) as a white solid: mp 71−72 °C (*n*-hexane); IR (KBr) 3400, 2920, 1620, 1570, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H), 7.20−7.28 (m, 1H), 7.38−7.50 (m, 3H), 7.80 (s, 1H), 8.01 (d, J = 7.7 Hz, 1H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.15, 103.59, 110.97, 119.36, 119.81, 120.71, 123.51, 124.61, 126.34, 129.04, 130.29, 136.32, 139.40; EI-MS *m*/*z* 261 (M^+ + 2, 96.4), 259 (M^+, 100), 180 (68.8), 152 (11.1), 90 (15.9). Anal. Calcd for $C_{13}H_{10}NBr$: C, 60.02; H, 3.87; N, 5.38. Found: C, 60.07; H, 3.87; N, 5.21.

1-Methoxy-3-methyl-9*H*-carbazole (Murrayafoline A) (10). DMF (10 mL), CuI (95%, 0.373 g, 1.86 mmol), and **3i** (0.242 g, 0.930 mmol) were added to a solution of metallic sodium (0.214 g, 18.6 mmol) in absolute MeOH (2.5 mL). The reaction mixture was refluxed (oil bath temperature = 120 °C) for 3 h under an argon atmosphere. After the reaction, EtOAc (40 mL) was added to the reaction mixture and the insoluble materials were filtered through Celite and washed with EtOAc. The filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on a column of silica gel using 10:1 *n*-hexane/EtOAc to give **10** (0.181 g, 92%) as a white powder: mp 51−53 °C (*n*-hexane) (lit.[22] 52−54 °C); IR (KBr) 3425, 1600, 1510, 1460, 1310, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H), 4.00 (s, 3H), 6.74 (s, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.34−7.46 (m, 2H), 7.47 (s, 1H), 8.02 (d, J = 7.9 Hz, 1H), 8.15 (br s, 1H). EI-MS *m*/*z* 211 (M^+, 100), 196 (71.7), 168 (37.5), 167 (27.0).

***N*-(4-Bromophenyl)-*N*-(2,5-dimethylphenyl)amine (11).** Pale yellow oil: IR (neat) 3400, 1590, 1490, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.27 (s, 3H), 5.31 (br s, 1H), 6.74−6.82 (m, 3H), 7.01 (s, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.40, 21.70, 111.75, 118.41, 120.53, 123.66, 126.17, 130.86, 132.05, 136.56, 140.21, 143.52; EI-MS *m*/*z* 277 (M^+ + 2, 98.5), 275 (M^+, 100), 194 (27.9), 181 (23.2); HR-MS *m*/*z* for $C_{14}H_{14}NBr$ calcd 275.0307, found 275.0310.

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