An Expedient Process for the Synthesis of 2-(*N*-Arylamino)benzaldehydes from 2-Hydroxybenzaldehydes via Smiles Rearrangement

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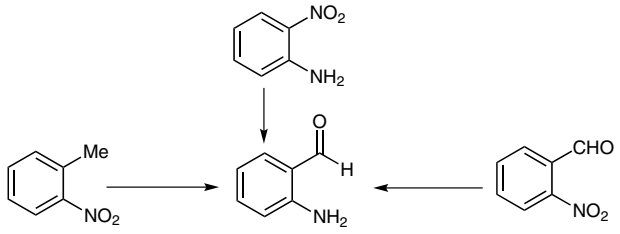
Dedicated to Professor Firouz Matloubi Moghaddam on his 62nd birthday

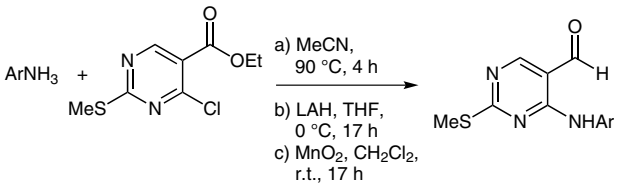
Abstract: This paper describes an efficient Smiles rearrangement process for the synthesis of 2-(*N*-arylamino)benzaldehyde derivatives with reasonable yields. A mechanism is proposed for the reaction course.

Key words: 2-(*N*-arylamino)benzaldehyde, 2-hydroxybenzaldehyde, Smiles rearrangement, O-alkylation

2-Aminobenzaldehyde derivatives are versatile and valuable building blocks for a number of biologically and pharmaceutically active compounds.[1] The synthesis and characterization of these important compounds have also been of interest in the field of coordination chemistry.[2] 2-Aminobenzaldehyde derivatives have both hydrogen-bonding and donor–acceptor properties but can be difficult to synthesize. For example, low yielding syntheses of the parent 2-aminobenzaldehyde have been reported from 2-nitroaniline (33%),[3] 2-nitrobenzaldehyde (40–50%),[4] and from 2-nitrotoluene (24%)[5] (Scheme 1).



Scheme 1



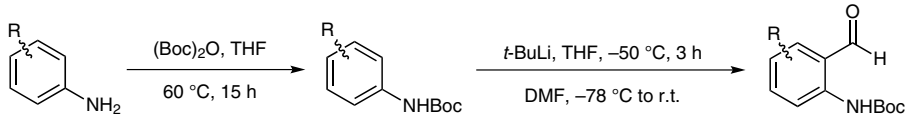
Scheme 2

In a recent patent, 4-(*N*-arylamino)pyrimidine-5-carbaldehydes were prepared by the procedure outlined in Scheme 2. However, the three-step protocol was restricted to 4-(*N*-arylamino)pyrimidine-5-carbaldehyde derivatives.[6] Alternatively, reduction of 2-aminobenzoic acids with borane followed by oxidation of the resultant 2-aminobenzyl alcohols with MnO_2 has been reported by Carter.[7] Formylation of substituted *N*-(*tert*-butoxycarbonyl) anilines using *t*-BuLi and dimethyl formamide at –78 °C affords *N*-Boc-2-aminobenzaldehyde derivatives (Scheme 3),[8] but this method suffers from poor substituent tolerance. In 2002, Apple reported the synthesis of *N*-alkyl-2-aminobenzaldehydes in moderate yield using quinolinium salts.[9]

To the best of our knowledge, there is no general method for the synthesis of 2-(*N*-arylamino)benzaldehydes in the literature. Therefore, a flexible protocol with wide substituent tolerance and mild reaction conditions is desirable for a general preparation of 2-(*N*-arylamino)benzaldehydes **5**. We proposed that the title compounds could be produced by reacting readily available 2-hydroxybenzaldehyde derivatives **4** with *N*-aryl 2-chloroacetamides **3**. This Letter presents our results based on the above approach (Scheme 4).

It is worth noting that structures **5** can be precursors of fenamic acid derivatives, nonsteroidal anti-inflammatory drugs which contain the basic structure **6** (Figure 1).[10]

To find the optimal conditions, synthesis of 2-(4-methylphenylamino)benzaldehyde (**5b**) in the presence of a base was chosen as a model reaction. A mixture of *N*-(4-methylphenyl) 2-chloroacetamide (**3**, 1 mmol), 2-hydroxy benzaldehyde (**4**, 1 mmol), and solvent (5 mL) was stirred under various reaction conditions. Our first experiment



Scheme 3

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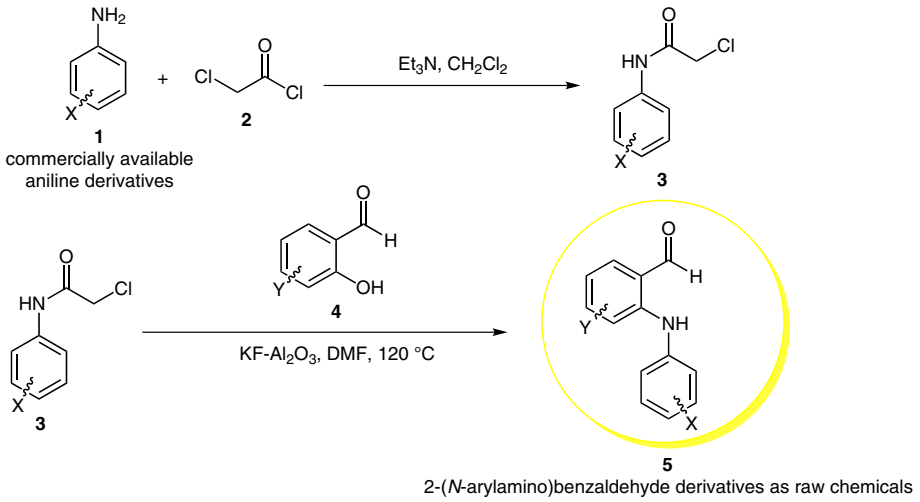


Scheme 4

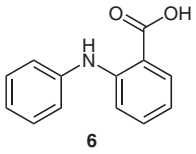


Figure 1

showed that the presence of a base such as K_2CO_3 or KF/Al_2O_3[11] was required to achieve the synthesis of **5b** and no reaction was observed when the reaction was performed without base. K_2CO_3 (59%) was less effective compared to KF/Al_2O_3 (72%).

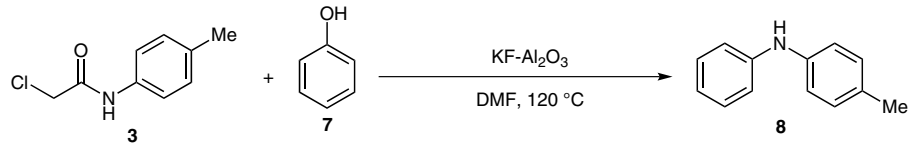
We then continued to optimize the model reaction by considering the efficiency of polar and nonpolar solvents. A polar solvent such as DMF was much better than a nonpolar solvent. The effect of temperature was also studied by carrying out the model reaction at room temperature, 90 °C, and 120 °C. It was observed that the yield was increased as the reaction temperature was raised to 120 °C. No desired product was observed when the reaction was performed at room temperature. Final optimized conditions involved KF/Al_2O_3 (150 mg), 2-chloro-*N*-arylacetamide **3** (1 mmol), 2-hydroxybenzaldehyde derivative **4** (1 mmol) in DMF (5 mL) at 120 °C for 14 hours. The structures of the products were confirmed by MS (EI), ^{1}H NMR and ^{13}C NMR, and CHN analysis.[12]

The ^{1}H NMR and ^{13}C NMR spectra of the product clearly indicated the formation of **5b**. The ^{1}H NMR spectrum contained a broad resonance at δ = 9.98 ppm correlating to the NH, a sharp singlet for the aldehyde proton at δ = 9.93 ppm and a singlet for the methyl protons at δ = 2.39 ppm. Intramolecular hydrogen bonding between the amine proton and the carbaldehyde group results in deshielding of the NH proton, a similar phenomenon also being observed in fenamic acid derivatives.[13] The ^{1}H-decoupled ^{13}C NMR spectrum of **5b** showed 12 distinct resonances in agreement with the proposed structure, with the aldehyde carbon appearing at δ = 194.2 ppm, 10 distinct resonances for the aromatic carbons between δ = 112.8–148.4 ppm and a resonance at δ = 21.0 ppm for the methyl carbon. The MS (EI) mass spectrum of **5b** clearly showed the presence of the molecular ion (211) [$M^{+\bullet}$] with elimination of the formyl moiety from $M^{+\bullet}$ to give *m/z* = 182 as the base peak (see Supporting Information).

To establish the generality of this method, we used a series of *N*-aryl 2-chloroacetamides and 2-hydroxybenzaldehydes to obtain the corresponding 2-(*N*-arylamino) benzaldehydes **5a**–**h** (Table 1). All the substrates consistently furnished the desired 2-(*N*-arylamino)benzaldehydes in good yields and were not limited to 2-hydroxybenzaldehydes; 2-hydroxynaphthalene-1-carboxaldehyde also afforded the desired products **5g** and **5h** in good yields (Table 1, entries 7 and 8).

The applicability of the present methodology was further extended by performing the reaction of phenol **7** with *N*-(4-methylphenyl) 2-chloroacetamide (**3**) in the presence of KF/Al_2O_3 (Scheme 5) to provide *N*-phenyl 4-methylaniline (**8**) in 40% yield. Further studies of the reaction between phenols and *N*-aryl 2-chloroacetamides for the formation of diarylamine derivatives are in progress.

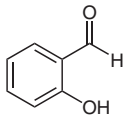
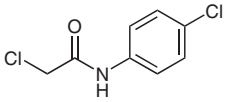
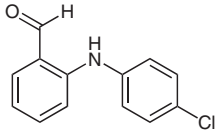
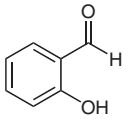
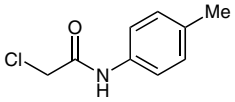
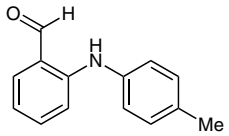
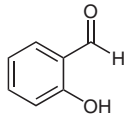
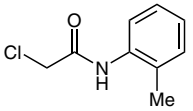
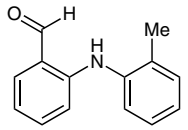
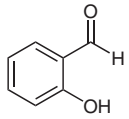
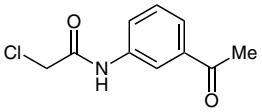
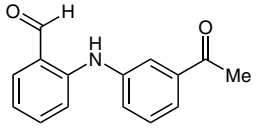
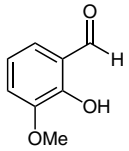
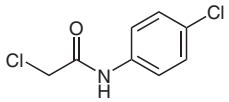
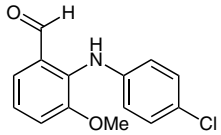
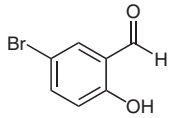
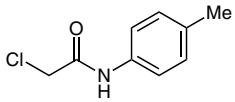
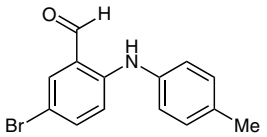
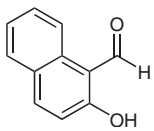
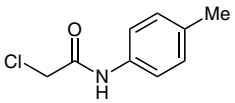
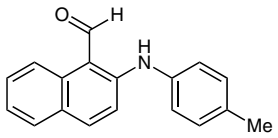
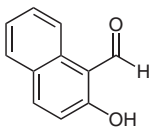
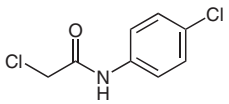
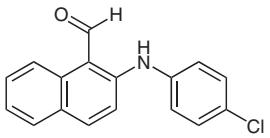
A possible reaction mechanism is proposed in Scheme 6. The first step is an O-alkylation of the 2-hydroxybenzal-

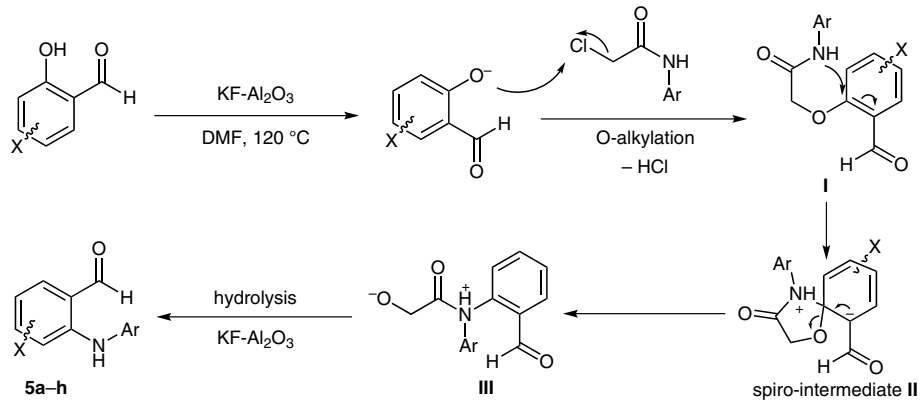


Scheme 5

dehyde with *N*-aryl 2-chloroacetamide affording aryloxyacetamide **I**. In the case of *N*-(4-chlorophenyl) 2-chloroacetamide, this intermediate was separated and its structure was confirmed by ^{1}H NMR analysis (see Supporting Information). The next step is the conversion of **I** into spiro intermediate **II** via Smiles rearrangement, replacing the oxygen atom on the benzene ring with a nitrogen atom.[14] Hydrolysis of compound **III** under the basic conditions then leads to the desired products. The intramolecular nucleophilic aromatic substitution of **I** is not favored by electron-withdrawing groups in the 2-chloro-*N*-aryl acetamide **3** (Table 1, entry 4). On the other hand, the electron-withdrawing aldehyde group in the 2-hydroxybenzaldehyde substrates **4** accelerates *ipso* nucleophilic aromatic substitution.

Table 1 Synthesis of 2-(*N*-Arylamino)benzaldehyde Derivatives

Entry	2-Hydroxy benzaldehyde **4**	2-Chloro-*N*-aryl acetamide **3**	Product	Yield (%)
1			 **5a**	74
2			 **5b**	72
3			 **5c**	55
4			 **5d**	43
5			 **5e**	58
6			 **5f**	63
7			 **5g**	60
8			 **5h**	61



Scheme 6

In conclusion, we report herein an efficient procedure for the synthesis of 2-(*N*-arylamino)benzaldehydes from 2-hydroxybenzaldehyde derivatives and *N*-aryl 2-chloroacetamides. Good yields and readily available starting materials are the key features of the present method.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) Saeidian, H.; Sadeghi, A.; Mirjafary, Z.; Moghaddam, F. M. *Synth. Commun.* **2008**, *38*, 2043.
(12) **General Procedure for the Synthesis of 2-(*N*-Arylamino)benzaldehydes 5a–h**
To a stirred suspension of KF/Al_2O_3 (150 mg) in DMF (5 mL) were added 2-hydroxy benzaldehyde **4** (1 mmol) and 2-chloro-*N*-arylacetamide **3** (1 mmol), and the reaction mixture was stirred at 120 °C for 14 h with progress of the reaction being monitored by TLC. After completion of the reaction, the mixture was poured into ice cold H_2O, stirred for 15 min, then extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by preparative TLC (eluent: PE–EtOAc, 6:1) to afford the desired compound **5a**–**h**.
Spectroscopic Data
***N*-(4-Chlorophenyl) 2-(2-Formylphenoxy)acetamide (I)**
^{1}H NMR (400 MHz, $CDC1_3$): δ = 10.11 (m, 2 H, CHO, NH), 7.87 (dd, J_1 = 8.80 Hz, J_2 = 2.0 Hz, 2 H), 7.82 (dd, J_1 = 9.20 Hz, J_2 = 1.60 Hz, 1 H), 7.68–7.75 (m, 1 H), 7.37 (dd, J_1 = 8.80 Hz, J_2 = 2.0 Hz, 2 H), 7.28 (m, 1 H), 7.01 (d, J = 8.0 Hz, 1 H), 4.72 (s, 2 H, CH_2) ppm.
2-(4-Chlorophenylamino)benzaldehyde (5a)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 10.00 (br s, 1 H, NH), 9.92 (s, 1 H, CHO), 7.59 (d, J = 8.0 Hz, 1 H), 7.33–7.42 (m, 3 H), 7.19–7.25 (m, 3 H), 6.88 (t, J = 7.80 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 194.35, 147.36, 138.34, 136.70, 135.64 (2 C), 129.53, 124.29, 119.59, 117.61, 112.82 ppm. MS (EI): *m/z* (%) = 233 (33), 231 (100) [M^+], 202 (74), 167 (91). Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05. Found: C, 67.18; H, 4.40; N, 5.95.
2-(4-Methylphenylamino)benzaldehyde (5b)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 9.98 (br s, 1 H, NH), 9.93 (s, 1 H, CHO), 7.58 (d, J = 8.80 Hz, 1 H), 7.38 (t, J = 7.80 Hz, 1 H), 7.17–7.23 (m, 5 H), 6.84 (t, J = 7.40 Hz, 1 H), 2.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 194.18, 148.39, 136.93, 136.61, 135.55, 135.35, 130.06, 123.69, 119.15, 116.77, 112.81, 21.00 ppm. MS (EI): *m/z* (%) = 211 (92) [M^+], 182 (100), 167 (43). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.50; H, 6.09; N, 6.70.
2-(2-Methylphenylamino)benzaldehyde (5c)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 9.97 (s, 1 H, CHO), 9.89 (br s, 1 H, NH), 7.60 (dd, J_1 = 9.20 Hz, J_2 = 1.60 Hz, 1 H), 7.32–7.40 (m, 3 H), 7.26 (t, J = 8.40 Hz, 1 H), 7.17 (t, J = 7.40 Hz, 1 H), 6.92 (t, J = 8.40 Hz, 1 H), 6.83 (t, J = 7.30 Hz, 1 H), 2.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 194.31, 148.42, 137.98, 136.49, 135.59, 133.28, 131.22, 126.12, 125.44, 124.75, 119.12, 114.64, 112.89, 18.05 ppm. MS (EI): *m/z* (%) = 211 (100) [M^+], 182 (74), 167 (39). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.48; H, 6.07; N, 6.56.

2-(3-Acetylphenylamino)benzaldehyde (5d)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 10.12 (br s, 1 H, NH), 9.93 (s, 1 H, CHO), 7.89 (d, *J* = 2.40 Hz, 1 H), 7.71–7.73 (m, 1 H), 7.62 (dd, J_1 = 7.60 Hz, J_2 = 1.80 Hz, 1 H), 7.41–7.49 (m, 3 H), 7.27 (t, *J* = 8.40 Hz, 1 H), 6.91 (t, *J* = 7.40 Hz, 1 H), 2.63 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 197.21. 194.44, 147.04, 140.34, 138.44, 136.76, 135.74, 129.72, 127.24, 124.08, 122.10, 119.74, 117.91, 112.85, 26.79 ppm. MS (EI): *m/z* (%) = 239 (100) [M^+], 210 (39), 196 (32), 168 (55), 167 (44). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.41; H, 5.35; N, 5.69.

2-(4-Chlorophenylamino)-3-methoxybenzaldehyde (5e)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 9.99 (s, 1 H, CHO), 8.77 (br s, 1 H, NH), 7.34 (dd, J_1 = 7.20 Hz, *J* = 2.40 Hz, 1 H), 7.18 (d, *J* = 8.80 Hz, 2 H), 7.11–7.13 (m, 2 H), 6.82 (d, *J* = 8.80 Hz, 2 H), 3.77 (s, 3 H, OCH_3) ppm. MS (EI): *m/z* (%) = 263 (34), 261 (100) [M^+], 234 (26), 232 (76) 183 (38). Anal. Calcd for $C_{14}H_{12}ClNO$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.30; H, 4.53; N, 5.24.

2-(4-Methylphenylamino)-5-bromobenzaldehyde (5f)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 9.91 (br s, 1 H, NH), 9.84 (s, 1 H, CHO), 7.66 (d, *J* = 2.40 Hz, 1 H), 7.39 (dd, J_1 = 8.80 Hz, J_2 = 2.20 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.40 Hz, 2 H), 7.04 (d, *J* = 8.80 Hz, 1 H), 2.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 192.90, 147.33, 138.15, 138.13, 136.35, 134.91, 130.19, 123.62, 120.30, 114.97, 107.62, 21.04 ppm. MS (EI): *m/z* (%) = 291 (96), 289 (99) [M^+], 262 (69), 260 (73), 167 (34). Anal. Calcd for $C_{14}H_{12}BrNO$: C, 57.95; H, 4.17; N, 4.83. Found: C, 57.77; H, 4.10; N, 4.91.

2-(4-Methylphenylamino)naphthalene-1-carbaldehyde (5g)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 11.60 (br s, 1 H, NH), 10.92 (s, 1 H, CHO), 8.37 (d, *J* = 8.40 Hz, 1 H), 7.74 (d, *J* = 9.20 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 7.20 Hz, 1 H), 7.21–7.35 (m, 6 H), 2.42 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 189.84, 150.15, 137.21, 136.25, 135.42, 135.02, 130.16, 129.35, 128.11, 126.65, 124.83, 123.13, 118.42, 115.25, 108.19, 21.06 ppm. MS (EI): *m/z* (%) = 261 (100) [M^+], 232 (85), 217 (53). Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.85; H, 5.61; N, 5.24.

2-(4-Chlorophenylamino)naphthalene-1-carbaldehyde (5h)
^{1}H NMR (400 MHz, $CDC1_3$): δ = 11.57 (br s, 1 H, NH), 10.93 (s, 1 H, CHO), 8.36 (d, *J* = 6.80 Hz, 1 H), 7.79 (d, *J* = 9.20 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.58 (t, *J* = 7.20 Hz, 1 H), 7.24–7.39 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 190.22, 149.11, 137.71, 137.38, 134.84, 130.58, 129.67, 129.40, 129.08, 126.94, 125.61, 123.49, 118.65, 114.84, 108.84 ppm. MS (EI): *m/z* (%) = 283 (34), 281 (100) [M^+], 252 (46), 217 (98). Anal. Calcd for $C_{14}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.29; H, 4.38; N, 4.80.

***N*-Phenyl 4-Methylaniline (8)**
^{1}H NMR (400 MHz, $CDC1_3$): δ = 7.26–7.31 (m, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.04–7.07 (m, 4 H), 6.93 (t, *J* = 7.40 Hz, 1 H), 5.66 (br s, 1 H, NH), 2.36 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDC1_3$): δ = 134.94, 140.28, 131.01, 129.92, 129.37, 120.38, 118.96, 116.93, 20.76 ppm.

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