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with dimethyl carbonate in continuous flow*

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## Graphical Abstract

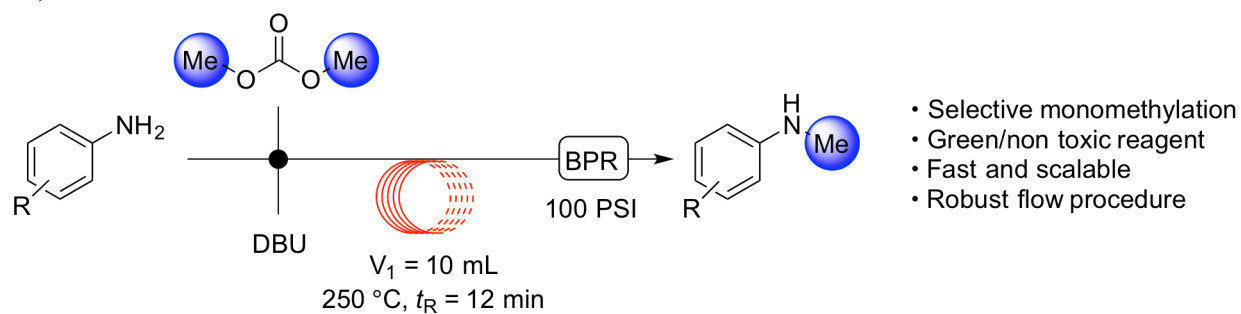
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### Selective *N*-monomethylation of primary anilines with dimethyl carbonate in continuous flow

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### ABSTRACT

Selective *N*-monomethylation of anilines has been achieved under continuous flow conditions using dimethyl carbonate as a green methylating agent in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. Our methodology takes advantage of the expanded process windows available in the continuous flow regime to safely induce monomethylation in superheated solvents at high pressure. We propose selective *N*-monomethylation is achieved via an *in situ* protection-deprotection pathway, which is supported by the observed reactivities of several putative reaction intermediates. The robust and scalable method was applicable to a broad range of primary aniline substrates including ortho-, meta-, and para-substituted anilines, as well as electron-rich and electron-deficient anilines. The synthetic precursor of diazepam, 5-chloro-2-(methylamino)benzophenone, was selectively synthesized under our optimized conditions.

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### Introduction

*N*-alkylanilines are ubiquitous motifs in the pharmaceutical and agrochemical industries.<sup>1</sup> In particular, *N*-methylanilines are found in a range of biologically active compounds such as diazepam, flabetapir, triafamone, and broflanilide (Figure 1).<sup>2</sup> *N*-alkylation reactions are common and essential transformations for the synthesis of pharmaceuticals and fine chemicals.<sup>3</sup> However, selective mono-*N*-alkylation of primary alkyl and aryl amines remains a challenging transformation due to the greater nucleophilicity of secondary amines compared to primary amines.<sup>4</sup> The synthesis of *N*-methylanilines is particularly challenging and the use of classical approaches for *N*-alkylation via reaction with alkyl halides or by reductive amination often results in the formation of mixtures of secondary and tertiary anilines.<sup>4, 5</sup> Often, lab-scale syntheses of *N*-methylanilines require multistep sequences involving the incorporation and removal of protecting groups or the installation and exhaustive reduction of a carbamate.<sup>6</sup> The difficulty associated with the selective *N*-monomethylation of primary anilines is often reflected in the price of *N*-methylanilines versus their primary aniline analogs. A 50- to 100-fold increase in the price per gram is not unusual for this seemingly simple functionalization.

The development of robust and selective methods for the selective *N*-monomethylation of primary anilines would greatly simplify the synthesis of *N*-methylanilines and several approaches have been reported. On the industrial scale, *N*-monomethylation of primary anilines is accomplished via reaction with methanol in the vapor phase using heterogeneous

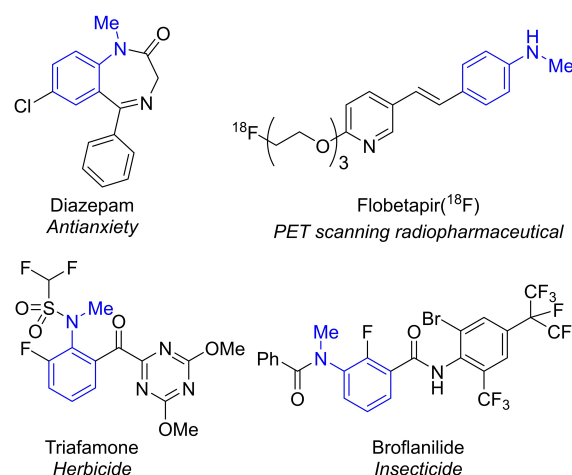
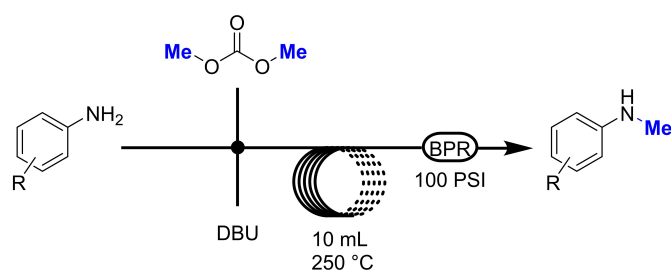


Fig. 1. Representative examples of bioactive *N*-monomethylanilines.



Scheme 1. Schematic diagram of the continuous flow system for the selective *N*-monomethylation of anilines.

transition metal catalysts at high temperatures (200-500 °C).<sup>7</sup> Homogeneous *N*-monomethylation reactions of primary anilines have also been developed, but require expensive ligands and transition metal catalysts.<sup>8</sup>

Dimethylcarbonate (DMC) is an inexpensive and green methylating reagent<sup>9</sup> that is commonly utilized in the methylation of carboxylic acids, arylacetoneitriles, phenols, indoles, and benzimidazoles.<sup>10</sup> DMC has been employed in the selective *N*-monomethylation of primary anilines in the presence of zeolite catalysts.<sup>11</sup> However, these reactions employ DMC in solvent quantities and require the use of an autoclave in order to heat the reaction past the boiling point of DMC (b.p. = 90 °C) and to accommodate the stoichiometric amount of CO<sub>2</sub> generated in the reaction. These challenges have limited the widespread application of DMC as a reagent for the selective *N*-monomethylation of primary anilines.

Continuous flow systems are an attractive platform for the selective *N*-monomethylation of anilines using DMC. The ability to incorporate back pressure regulators (BPR) and the small volume of the flow reactor enables reactions to be safely operated at temperatures and pressures which would be inaccessible in traditional batch systems without specialized equipment (e.g., autoclave).<sup>12</sup> Furthermore, gaseous byproducts can be safely contained in the pressurized continuous flow system and then undergo controlled separation from the liquid phase upon passing through the back pressure regulator.<sup>13</sup> Herein, we report the development of an efficient and selective *N*-methylation of primary anilines with environmentally benign DMC in a commercially available Vapourtec E-series continuous flow system (Scheme 1).

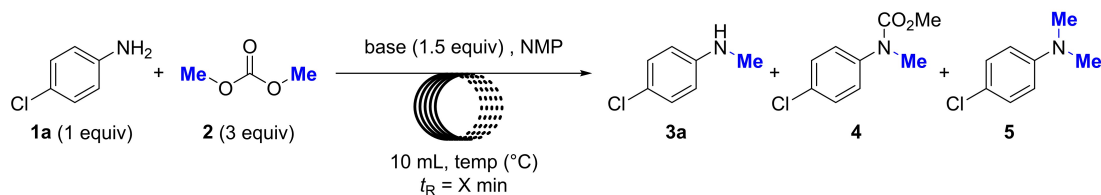
## 1. Results/Discussion

Initial optimization studies on the continuous *N*-monomethylation of primary anilines with DMC were performed using 4-chloroaniline (**1a**) as a model substrate (Table 1). In a Vapourtec E-series continuous flow platform, a stream of **1a** in *N*-Methyl-2-pyrrolidone (NMP) was mixed with streams of DMC (3 equiv) in NMP and base (1.5 equiv) in NMP using a cross

mixer. The combined reagent stream was then transported through a high temperature coiled tube reactor (10 mL, stainless steel, 0.03" i.d.), which was equipped with a back pressure regulator (100 psi) to help control the release of the CO<sub>2</sub> produced in the reactor. Preliminary studies identified 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the optimal base for the reaction and all optimization studies were performed using DBU (Entries 1 – 7). However, other bases, such as triethylamine, were found to be competent in the reaction, albeit lower yielding (Entry 8). The continuous *N*-monomethylation of **1a** was found to be highly temperature dependent. When the reaction was performed at 90 °C (the boiling point of DMC), no *N*-methyl aniline (**3a**) was observed during a 12 minute residence time (Entry 1). Increasing the reaction temperature to 150 °C showed trace conversion to carbamate **4** but no formation of **3a** (Entry 2). Further heating to 200 °C resulted in increased formation of carbamate **4** and some formation of the desired *N*-methylaniline **3a** (Entry 3). Best results were obtained at 250 °C, providing *N*-methylaniline **3a** in 88% yield with 12% of carbamate **4** and no overalkylation byproducts **5** (Entry 4). It was found that 12 minutes was an optimal residence time, as increasing or decreasing residence time resulted in decreased yields of **3a** (Entries 5 – 7). At a residence time of 20 minutes, trace amounts *N,N*-dimethylaniline **5** were observed (Entry 7). Under optimized conditions (12 minutes, 250 °C), a throughput of 3.7 g/h of **3a** was achieved.

The increased ratio of **4** to **3a** at lower temperature and shorter residence time is consistent with formation of **4** as the initial product of the reaction (Scheme 2). *N*-methylaniline **3a** could then be formed by an *in situ* thermal decarboxylation of **4**, analogous to a solvent-free thermal *tert*-butyloxycarbonyl (Boc) deprotection.<sup>14</sup> Based on these observations, we propose that the reaction sequence begins by reaction of aniline **1a** with DMC to form carbamate **6**, followed by methylation of the carbamate via reaction with a second equivalent of DMC in the presence of DBU to form **4**. Carbamate **4** then undergoes a thermal decarboxylation to provide *N*-methylaniline **3a**. In support of this reaction pathway, we found that **4** decomposes to form **3a** at 250

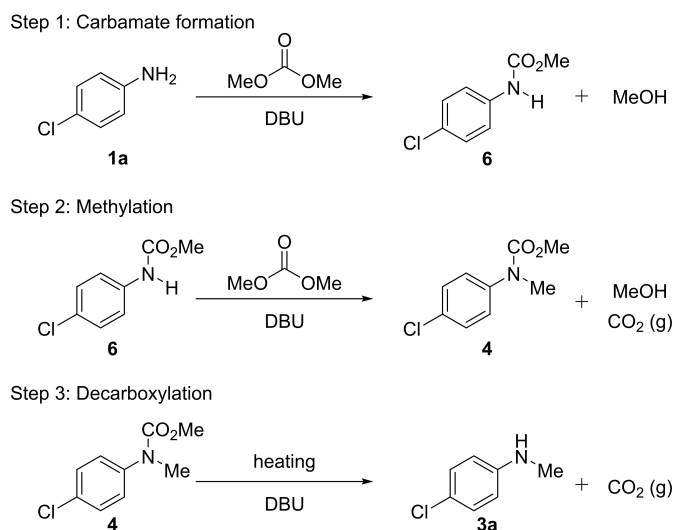
**Table 1.** Optimization of selective *N*-monomethylation of 4-chloroaniline.<sup>a</sup>



Entry	Base	Temp (°C)	<i>t<sub>R</sub></i> (min)	Yield <b>3a</b> (%) <sup>b</sup>	Yield <b>4</b> (%) <sup>b</sup>	Yield <b>5</b> (%) <sup>b</sup>
1	DBU	90	12	0	0	0
2	DBU	150	12	0	trace	0
3	DBU	200	12	26	63	0
4	DBU	250	12	88	12	0
5	DBU	250	5	55	17	0
6	DBU	250	16	61	7	0
7	DBU	250	20	68	15	<5
8	TEA	250	12	15	30	0

<sup>a</sup>Reactions were carried out using a Vapourtec E-series flow chemistry system. Reaction conditions: **1a** (20 mmol, 2 M in NMP), DMC (60 mmol, 6 M in NMP) and base (30 mmol, 3 M in NMP) were introduced to a 10 mL stainless steel reactor tubing at a flow rate for the designated residence time. The system was equilibrated for 1.5x the residence time. <sup>b</sup>Calculated by GC analysis using methyl benzoate as an internal standard.

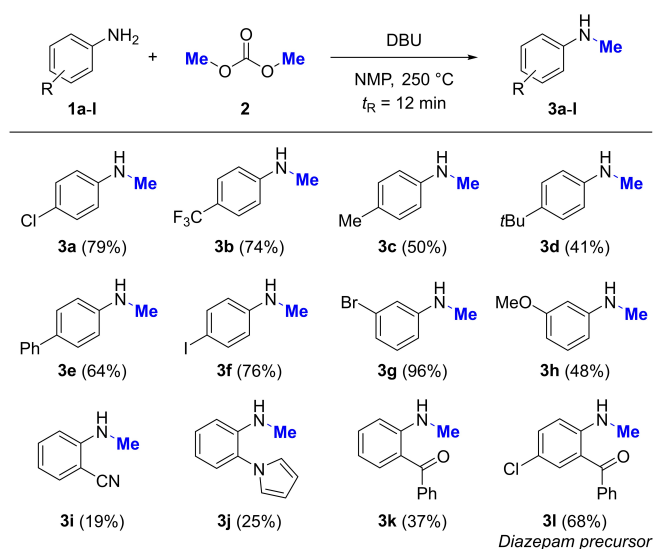
°C and **6** reacts with DMC and DBU to form **3a**. These results suggest that anilines preferentially react with DMC to form carbamates under our reaction conditions and methylation predominantly occurs by reaction of DMC with a carbamate.



**Scheme 2.** Proposed pathway of selective *N*-monomethylation of anilines.

We next explored the scope of our selective *N*-monomethylation reaction with a variety of aniline substrates (Table 2). It was found that substitution was generally tolerated at the para- (**3a** – **3f**), meta- (**3g** and **3h**), and ortho-positions (**3i** – **3l**). However, sterically hindered anilines such as 2,5-dimethylaniline did not undergo methylation under our reaction conditions. It was also found that both electron-deficient (**3a**, **3b**, **3i**, **3k** and **3l**) and electron-rich (**3c**, **3d**, **3e**, **3h**, **3j** and **3l**) substrates were tolerated under the conditions. *N*-methylaniline **3l** has been employed as a starting point in several syntheses of diazepam but is significantly more expensive than the corresponding primary aniline.<sup>2a,15</sup> Under our optimized continuous flow conditions, **3l** was readily generated in good yield without the formation of any overalkylation byproducts.

**Table 2.** Substrate scope.<sup>a</sup>



<sup>a</sup>Isolated yield of the *N*-monomethylaniline.

## 2. Conclusion

In conclusion, the selective *N*-monomethylation of primary anilines has been accomplished using a commercial continuous flow platform. The reaction employs DMC as an inexpensive and environmentally friendly methylating reagent and relies on an *in situ* protection/deprotection strategy to achieve excellent selectivity for monomethylation. The continuous flow system enables safe and robust *N*-monomethylation of anilines at high temperature with a throughput of 3.7 g/h. Aniline substitution is generally tolerated in the reaction and selective *N*-monomethylation can be achieved with both electron-rich and electron-deficient anilines. This methodology was successfully employed to produce an intermediate in the synthesis of diazepam in good yield at low cost.

## 3. Experimental Section

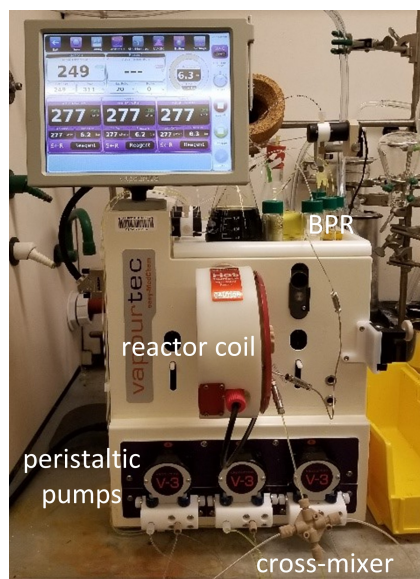
### 3.1. General

Commercially available reagents were used without additional purification. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated silica gel (EM 60 F254) plates. Visualization was accomplished with UV light (254 nm) and exposure to potassium permanganate solution followed by heating. Column chromatography was carried out on a Biotage Isolera flash chromatography system using SNAP KP-Sil or Ultra-Sil columns (silica gel, average particle size 50  $\mu$ m and 25  $\mu$ m spherical respectively). Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra and carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were obtained on a Bruker 400 MHz NMR instrument (400 and 101 MHz, respectively). Chemical shifts for proton are reported in parts per million (ppm) downfield from tetramethylsilane ( $\delta$  = 0.00 ppm) and are referenced to residual protium in CDCl<sub>3</sub> (7.26 ppm). Chemical shifts for carbon are reported in ppm downfield from tetramethylsilane ( $\delta$  = 0.00 ppm) and are referenced to residual carbon in CDCl<sub>3</sub> (77.0 ppm). The following designations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were obtained on an Agilent Cary 630 FT-IR spectrometer equipped with an ATR (attenuated total reflectance) accessory. The following designations are used to describe intensities: s (strong), m (medium), w (weak), br (broad). High-resolution mass spectrometry data were acquired in the Department of Chemistry Instrumentation Facility, Massachusetts Institute of Technology on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR Mass Spectrometer. Gas chromatography (GC) was performed on an Agilent 5870 GC (HP-5 column) with a flame ionization detector.

### 3.2. General procedure for the selective *N*-monomethylation of anilines in continuous flow.

Selective *N*-monomethylation reactions were performed in a Vapourtec E-series continuous flow system equipped with a high temperature tube reactor (10 mL, stainless steel, 0.03" i.d., Figure 2) and a membrane back pressure regulator (Zaiput). Stock solutions of aniline (20 mmol, 1.0 equiv, 2M), DMC (5.05 mL, 60 mmol, 3.0 equiv, 6 M), and DBU (4.47 mL, 30 mmol, 1.5 equiv, 3 M) were prepared in oven-dried 10 mL volumetric flasks using NMP as the solvent. The solutions were transferred to screw-thread vials with septum caps and reagents were pumped directly from the vials. After the high temperature coiled tube reactor was heated to 250 °C, peristaltic pumps (Vapourtec V3) were used to pump the reactant solutions into the system (0.277 mL/min each for a 12 min residence time). The solutions were mixed with a cross-mixer (0.4" i.d.), passed through the high temperature coiled tube reactor. Upon exiting the reactor, the

reaction stream was passed through a short segment of stainless steel tubing to enable the reaction to cool and then exited the system by passage through the back pressure regulator (**Note:** PFA fittings should not be used at the exit of the reactor as they will deform due to the high temperature of the reaction stream and cause leaks in the system). After the flow system was equilibrated for 18 minutes, the product stream was collected for 5 min (2.77 mmol of aniline). The crude mixture was dissolved in ethyl acetate and washed with brine. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (Biotage 25 g Ultra-sil, 3–15% ethyl acetate in hexanes) to afford the desired product.



**Figure 2.** Photographs of E-series flow platform.

### 3.2.1. 4-chloro-*N*-methylaniline (**3a**)

307 mg (79%); yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20 – 7.07 (m, 2H), 6.62 – 6.50 (m, 2H), 3.85 (br s, 1H), 2.82 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  147.6, 129.0, 122.0, 113.6, 30.9.  $^1\text{H}$  NMR spectra is in agreement with that reported in the literature.<sup>16</sup>

### 3.2.2. *N*-methyl-4-(trifluoromethyl)aniline (**3b**)

359 mg (74%); clear oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (d,  $J$  = 8.4 Hz, 2H), 6.68 (d,  $J$  = 8.0 Hz, 2H), 4.36 (br s, 1H), 2.88 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  150.7, 126.6 (q,  $J$  = 3.9 Hz), 126.2, 123.5, 112.2, 30.8. The  $^1\text{H}$  NMR spectra is in agreement with that reported in the literature.<sup>16</sup>

### 3.2.3. *N*,4-dimethylaniline (**3c**)

168 mg (50%); clear oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.03 (d,  $J$  = 7.9 Hz, 2H), 6.56 (d,  $J$  = 8.2 Hz, 2H), 2.83 (s, 3H), 2.27 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  146.8, 129.7, 126.8, 112.9, 31.3, 20.4. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are in agreement with those reported in the literature.<sup>17</sup>

### 3.2.4. 4-(*tert*-butyl)-*N*-methylaniline (**3d**)

183 mg (41%); clear oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.24 (m, 2H), 6.81 – 6.72 (m, 2H), 3.37 (br s, 1H), 2.90 – 2.81 (s, 3H), 1.29 (s, 9H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  146.7, 140.2, 125.9, 112.4, 33.8, 31.5, 31.1. IR (neat,  $\text{cm}^{-1}$ ) 3410 (m), 3054 (w), 2959 (m), 2900 (m), 2868 (m), 2810 (w), 1700 (w), 1617 (m), 1520 (s), 1488 (m), 1459 (m), 1392 (w), 1362 (m), 1348 (m), 1303 (m), 1262 (m), 1193 (m), 1155 (m), 1113 (w), 1058 (w), 931 (w), 819 (s), 777 (w), 731 (w), 702 (w). HRMS (m/z)  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{17}\text{N}$ , 164.1434; found, 164.1435.

### 3.2.5. *N*-methyl-[1,1'-biphenyl]-4-amine (**3e**)

323 mg (64%); yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 (d,  $J$  = 7.0 Hz, 2H), 7.49 (d,  $J$  = 8.4 Hz, 2H), 7.40 (t,  $J$  = 7.6 Hz, 2H), 7.27 (t,  $J$  = 7.4 Hz, 1H), 6.79 (d,  $J$  = 7.6 Hz, 2H), 3.42 (br s, 1H), 2.91 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  147.5, 141.1, 131.4, 128.6, 128.0, 126.4, 126.2, 113.6, 31.4. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are in agreement with those reported in the literature.<sup>18</sup>

### 3.2.6. 4-iodo-*N*-methylaniline (**3f**)

490 mg (76%); yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 – 7.40 (m, 2H), 6.47 – 6.44 (m, 2H), 3.37 (br s, 1H), 2.81 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  137.8, 115.2, 31.0. IR (neat,  $\text{cm}^{-1}$ ) 3418 (m), 3182 (w), 2984 (w), 2922 (w), 2879 (m), 2811 (m), 2571 (w), 2384 (w), 2295 (w), 2118 (w), 1869 (w), 1590 (w), 1494 (s), 1430 (w), 1389 (m), 1314 (s), 1293 (m), 1257 (s), 1180 (s), 1154 (m), 1111 (w), 1067 (w), 1051 (m), 993 (m), 807 (s), 751 (m), 692 (m). HRMS (m/z)  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_7\text{H}_8\text{IN}$ , 233.9774; found, 233.9782.

### 3.2.7. 3-bromo-*N*-methylaniline (**3g**)

490 mg (96%); yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.03 (t,  $J$  = 8.0 Hz, 1H), 6.85 – 6.82 (m, 1H), 6.77 (t,  $J$  = 2.0 Hz, 1H), 6.57 – 6.54 (m, 1H), 4.07 (br s, 1H), 2.82 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  150.0, 130.4, 123.3, 120.4, 115.2, 111.6, 30.8. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are in agreement with those reported in the literature.<sup>17</sup>

### 3.2.8. 3-methoxy-*N*-methylaniline (**3h**)

183 mg (48%); yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (t,  $J$  = 8.1 Hz, 1H), 6.34 – 6.28 (m, 2H), 6.23 (q,  $J$  = 2.3 Hz, 1H), 4.07 (br s, 1H), 3.79 (s, 3H), 2.84 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  160.8, 149.9, 130.0, 106.2, 103.2, 99.0, 55.1, 31.2. The  $^1\text{H}$  NMR spectra is in agreement with that reported in the literature.<sup>19</sup>

### 3.2.9. 2-(methylamino)benzotrile (**3i**)

70 mg (19%); yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 (dt,  $J$  = 7.5, 1.9 Hz, 2H), 6.76 (td,  $J$  = 7.2, 6.7 Hz, 2H), 4.17 (br s, 1H), 2.95 (d,  $J$  = 2.2 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  151.0, 134.3, 132.8, 117.6, 116.0, 109.7, 95.2, 30.6. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are in agreement with those reported in the literature.<sup>17</sup>

### 3.2.10. *N*-methyl-2-(1*H*-pyrrol-1-yl)aniline (**3j**)

119 mg (25%); clear oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (td,  $J$  = 7.8, 1.6 Hz, 1H), 7.17 (dd,  $J$  = 7.6, 1.6 Hz, 1H), 6.92 – 6.77 (m, 4H), 6.35 (t,  $J$  = 2.1 Hz, 2H), 5.20 (br s, 1H), 2.77 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  144.5, 128.9, 127.3, 126.9, 121.9, 116.5, 110.8, 109.3, 30.3. IR (neat,  $\text{cm}^{-1}$ ) 3422 (m), 2918 (m), 2880 (m), 2817 (m), 1741 (w), 1606 (m), 1586 (m), 1516 (s), 1484 (m), 1317 (s), 1291 (m), 1265 (w), 1247 (w), 1168 (m), 1117 (w), 1094 (m), 1065 (m), 1038 (w), 1013 (m), 923 (m), 842 (w), 801 (w), 722 (s). HRMS (m/z)  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_2$ , 173.1073; found, 173.1069.

### 3.2.11. 2-(methylamino)phenyl(phenyl)methanone (**3k**)

215 mg (37%); yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 – 7.57 (m, 2H), 7.55 – 7.48 (m, 2H), 7.48 – 7.40 (m, 3H), 6.91 (d,  $J$  = 8.4 Hz, 1H), 6.64 (t,  $J$  = 7.6 Hz, 1H), 2.99 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  199.1, 151.2, 140.1, 135.3, 135.0, 130.9, 129.0, 128.7, 128.1, 118.4, 115.2, 112.6, 30.4. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are in agreement with those reported in the literature.<sup>20</sup>

### 3.2.12. (5-chloro-2-(methylamino)phenyl(phenyl)methanone (**3l**)

461 mg (68%); yellow solid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 – 7.58 (m, 2H), 7.57 – 7.52 (m, 1H), 7.51 – 7.43 (m, 3H), 7.37 (dd,  $J$  = 9.0, 2.6 Hz, 1H), 6.83 (d,  $J$  = 8.9 Hz, 1H), 2.97 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  198.1, 149.9, 139.4, 134.8, 133.9, 131.3, 129.0, 128.3, 119.6, 118.9, 113.9, 30.3. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are in agreement with those reported in the literature.<sup>21</sup>

## 3.3. Characterization of reaction intermediates.

### 3.3.1. methyl (4-chlorophenyl)(methyl)carbamate (4)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35 – 7.28 (m, 2H), 7.22 – 7.13 (m, 2H), 3.71 (s, 3H), 3.28 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 155.9, 141.8, 129.0, 126.9, 53.0, 37.6.

### 3.3.2. methyl (4-chlorophenyl)carbamate (6)

4-Chloroaniline (6.4 g, 50 mmol) and methyl chloroformate (5.8 mL, 75 mmol) were added to a solution of sodium carbonate (10.6 g, 100 mmol) in water (100 mL) and dichloroethanol (100 mL). The reaction mixture was stirred at 40 °C for 3 hr. The organic layer was separated, washed with 1 M HCl solution and brine. The organic layer was concentrated to provide the carbamate **6** in 99% (9.2 g) yield as a white solid.<sup>22</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.58 (br s, 1H), 3.78 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 153.9, 136.4, 129.0, 128.4, 119.9, 52.4. The <sup>1</sup>H NMR spectra is in agreement with that reported in the literature.<sup>22</sup>

### 3.4. Supporting experiments for the reaction pathway of the *N*-monomethylation of anilines.

#### 3.4.1. Formation of **3a** from **4**.

General procedure was followed with carbamate **4** (20 mmol, 1.0 equiv, 2 M) and DBU (30 mmol, 1.5 equiv, 3 M) with no DMC. 359 mg (92%); yellow oil.

#### 3.4.2. Formation of **3a** from **6**.

General procedure was followed with carbamate **6** (20 mmol, 1.0 equiv, 2 M) and DMC (40 mmol, 2.0 equiv, 4 M), and DBU (30 mmol, 1.5 equiv, 3 M). 363 mg (93%); yellow oil.

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