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Continuous Flow Nucleophilic Aromatic Substitution with Dimethylamine Generated in Situ by Decomposition of DMF

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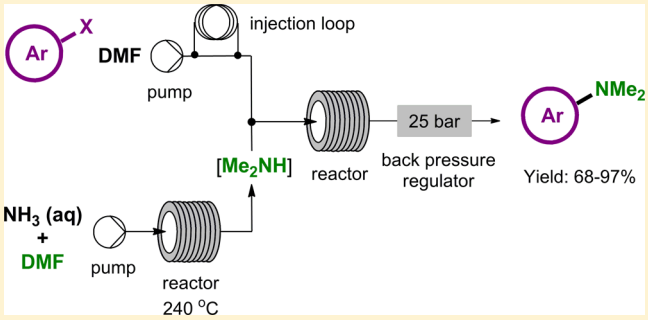
Supporting Information

ABSTRACT: A safe, practical, and scalable continuous flow protocol for the in situ generation of dimethylamine from DMF followed by nucleophilic aromatic substitution of a broad range of aromatic and heteroaromatic halides is reported.



Aryldimethylamines can be prepared by nucleophilic aromatic substitution (S_NAr) of aryl or heteroaryl halides with dimethylamine. However, because of the volatile nature of this reagent and the high temperatures or long reaction times often required,[1] outgassing from open flask reactors or pressure build-up under sealed-tube conditions can be problematic. Rather than using a premade solution, dimethylamine can be produced in situ from thermal decomposition of DMF,[2] a process that can be catalyzed by acids or bases.[3] Substitution of aryl halides using this method often involves refluxing the substrate in DMF for several hours or days.[4] Although the reaction rate can be improved by microwave-assisted heating in a sealed tube,[5] the pressure build-up poses a serious safety concern and complicates scale-up. We envisaged that continuous flow chemistry would overcome this problem while maintaining the advantages of sealed-tube microwave technology, including fast and efficient heat transfer and safe heating above the boiling point of the solvent with no outgassing of the generated dimethylamine.[6] The small volume of a flow reactor and the fact that the system is inherently open to the environment virtually eliminates any risk of explosion due to excessive pressure build-up. A flow process can furthermore be scaled up without reoptimizing the reaction conditions simply by running the system for a longer period of time.[6a,b,d] Herein, we report our findings resulting in the development of a safe, convenient, scalable, and versatile method for the conversion of aryl halides to aryldimethylamines using DMF and aqueous ammonia as the only solvents/reagents required.

Inspired by our previous finding that aqueous ammonia efficiently promotes DMF decomposition,[7] we launched a pilot study using sealed-tube microwave conditions to investigate the effect of various acid and base additives on the rate of nucleophilic aromatic substitution of 2-chloro-3-nitropyridine to form *N*,*N*-dimethyl-3-nitropyridin-2-amine (Table 1). The substrate and the additive were dissolved in DMF and allowed to react at 150 °C for 30 min using microwave heating. The results of this study (Table 1) showed that basic additives were superior to acidic ones as promoters of DMF decomposition. Of these, ammonia was clearly the most efficient, with the ammonia adduct as the only side product. This side reaction might only pose a problem for the more reactive substrates, as it has been shown previously that ammonia does not react with 4,7-dichlorophenanthroline.[7]

Transferred to a continuous flow system, the additives produced essentially the same ranking, with ammonia being by

Table 1. Effect of Additives on Decomposition of DMF

additive	batch[a,b] (%)	flow[b,c] (%)
PTSA (0.05 M)	5 (93)	29 (71)
AcOH (0.05 M)	5 (95)	11 (87)
NH_4Cl (0.05 M)	10 (89)	32 (66)
K_2CO_3 (aq, 0.25 M)[d]	45 (26)	precipitation
NH_3 (aq, 2.5 M)[e]	76 (0)	93 (7)

[a]Microwave-assisted heating (150 °C, 30 min). Yields were determined by HPLC. [b]Flow rate: 0.500 mL/min, volume: 10 mL, residence time: 20 min., temperature: 240 °C. Yields were determined by LC−MS. [c]The amount of remaining 2-chloro-3-nitropyrindine is shown in parentheses. [d]0.5 M K_2CO_3 (aq) and DMF (1:1). [e]12.4 M NH_3 (aq) and DMF (1:4).

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far the most efficient (Table 1). No trace of reaction with ammonia was observed under flow conditions, indicating a significantly better reaction control compared to the microwave-assisted batch synthesis.

The optimal temperature and concentration for ammonia-promoted generation of dimethylamine was investigated using the system outlined in Scheme 1. A solution of 2-chloro-3-nitropyridine (1.0 M in DMF) was loaded into a 1.043 mL injection loop and injected into a stream of DMF (0.167 mL/min). This stream was mixed with a stream of pure DMF or aqueous ammonia (12.4 M) in DMF (1:4 or 1:9 v/v at 0.167 mL/min) and passed through a heated tube reactor (10 mL, residence time: 30 min). The system was pressurized to 25 bar to prevent boiling and outgassing. Full conversion was observed at a temperature of 250 °C using ammonia concentrations down to 1.24 M (Table 2).

Scheme 1. One-Step Method for DMF Decomposition and S_NAr

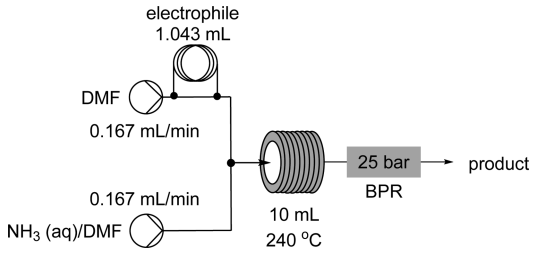


Table 2. Optimization of DMF Decomposition under Flow Conditions

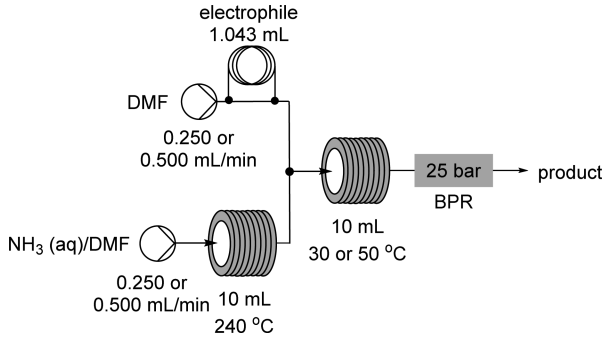
temp (°C)	NH_3 conc (M)[a]	yield[b] (%)
150	0	20
150	2.48	69
200	2.48	80
250	2.48	100
250	1.24	100

[a]12.4 M NH_3 (aq) mixed with DMF (1:4 or 1:9). [b]Determined by reaction with 2-chloro-3-nitrophyridine, analyzed by LC−MS.

Having identified optimal conditions for the test reaction, we proceeded with exploring the general scope of the method. Thus, various substrates were subjected to the reaction conditions of this one-step method comprising generation of dimethylamine and further nucleophilic substitution in the same reactor (Scheme 1). A solution of the substrate (0.25−1.0 M in DMF depending on solubility, see Table 3) was injected as described above (1.24 M ammonia in DMF, 30 min residence time at 240 °C). For convenience, 240 °C was chosen as the reactor temperature, as the stabilization time required for 250 °C (the maximum system temperature) was significantly longer. The output stream was collected and the product was isolated by aqueous workup and flash chromatography, unless otherwise stated (Table 3). Good to excellent yields for dimethylamine substitution of 2- and 4-chloropyridines, chloropyrimidines, and chloro- and bromoquinolines (entries 1−3 and 5−7) were obtained under these conditions. Electron-deficient chloro- and fluorobenzenes (entries 8 and 9) as well as 2-chloro- or bromoazoles (entries 11−13) were also excellent substrates for this procedure.

Although efficient for these aryl halides, the harsh conditions of this one-step method was found to decompose more sensitive substrates and cause side reactions when using reactants carrying functional groups such as nitriles (entry 14). A two-step procedure was therefore developed (Scheme 2)

Scheme 2. Two-Step Method for DMF Decomposition and S_NAr



where the dimethylamine generation and the nucleophilic substitution were performed in separate reactors to allow independent variation of temperatures and reaction times. Aqueous ammonia in DMF (1:9 v/v) was pumped at a flow rate of 0.250 mL/min through a stainless steel reactor at 240 °C (residence time: 40 min) to preform the dimethylamine after which it was mixed with a solution of the electrophile (0.25 or 0.50 M in DMF). The mixture was passed through a PFA reactor at 30−50 °C (residence time: 20 min), where the substitution took place. In most cases, 30 °C was sufficient to effect the substitution reaction. Using this two-step procedure, nitriles (entries 15−16) and ethyl esters (entry 17) incompatible with the harsh conditions of the one-step procedure were tolerated, and good to excellent results were obtained for a range of electron-deficient aryl and heteroaryl fluorides and chlorides (entries 18−22). Notably, some substituted 1-halo-2-nitrobenzenes that decomposed with the one-step method (e.g., entries 14 and 22) gave excellent yields using the milder two-step method (entries 15 and 23). On the other hand, the chloropyrimidine substitution benefited from the high temperature of the one-step method (entry 3), whereas no conversion to product was observed with the two-step method (entry 4). For relatively undemanding substrates (e.g., entries 9 and 10), both methods resulted in good to excellent yields.

To demonstrate the postulated advantages of flow chemistry in scale-up, i.e., no safety issues due to pressure build-up, and no boiling or outgassing, a solution of 4-chloro-6-methylpyrimidin-2-amine (0.50 M in DMF, 135 mL) was subjected to the one-step method. Apart from the modification that the reactant solution was fed directly through the pump into the system instead of being loaded into an injection loop, no conditions were changed or optimized to run this reaction on a 129 times larger scale (Scheme 3). The synthesis yielded 8.8 g (83%) corresponding to a space time yield of 65 g h^{-1} L^{-1} of N^4,N^4,6-trimethylpyrimidine-2,4-diamine after semiautomatic flash chromatography, which is consistent with the yield observed when the synthesis was performed on small scale (entry 3, Table 3).

In conclusion, we have developed a flow protocol for the in situ formation of dimethylamine from DMF to be used in the substitution of activated aromatic and heteroaromatic halides.

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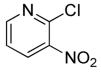
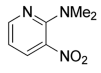
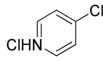
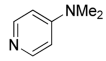
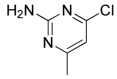
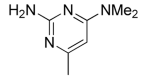
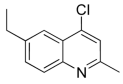
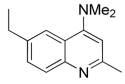
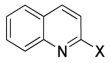
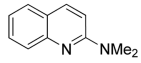
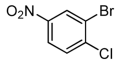
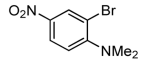
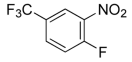
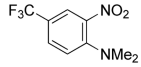
Table 3. Scope of One-step (A) and Two-Step (B) Method for DMF Decomposition and S_NAr

entry	method	reactant	product	conc (M)[a]	isolated yield (%)
1	A			1.0	59[b]
2	A			0.5	78[c]
3	A			0.5	74
4	B				0
5	A			1.0	82
6 (X = Cl)	A			1.0	89
7 (X = Br)	A				77
8	A			1.0	87
9	A			1.0	78
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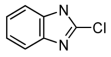
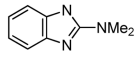
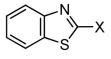
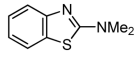
11	A			0.5	92
12 (X = Cl)	A			0.5	86
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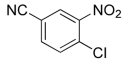
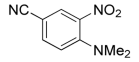
14	A			0.5	14[d]
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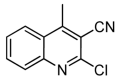
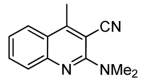
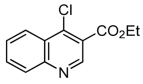
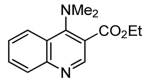
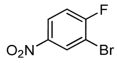
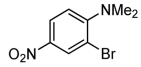
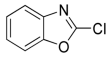
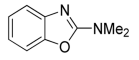
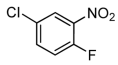
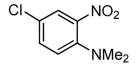
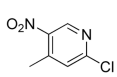
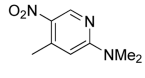
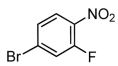
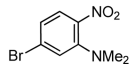
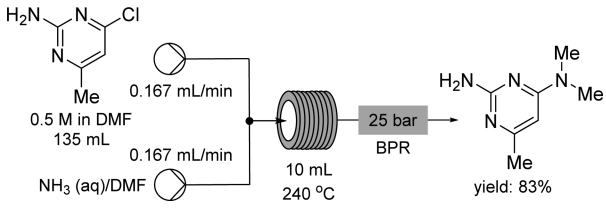
16	B			0.5	68
17	B[e]			0.5	79
18	B			0.25	97[c]
19	B			0.5	94[c]
20	B			0.25	79
21	B			0.5	92
22	A			0.5	0
23	B[f]				97[c]

[a]Concentration of reagent in injection loop. [b]Low yield due to difficulties isolating the product. [c]Products pure after aqueous workup, i.e., no column chromatography. [d]Estimated by dividing the product peak area by the total peak area in the UV trace of LC–MS. [e]Temperature of second reactor: 50 °C. [f]Flow rate of each stream: 0.500 mL/min.

Scheme 3. Scale-up



The synthesis is easy to perform, makes use of inexpensive reagents, is scalable, and benefits from the improved safety profile of the continuous flow reaction. The temperature of the substitution reaction can be varied independently of the decomposition of DMF, allowing a broader scope and resulting in good to excellent yields for a number of electrophiles. Notably, the reaction is safely and easily scaled up to give high yields with no additional optimization.

EXPERIMENTAL SECTION

General Methods. UPLC-MS was performed with PDA detector (operating at 254 nm), ELS detector and TQ-MS equipped with APPI-source operating in positive-ion mode. High-resolution mass spectra were recorded using APPI ionization.

Effect of Additives in Microwave Experiments. A microwave vial was charged with 2-chloro-3-nitropyridine (0.079 g, 0.5 mmol) and one of the following additives: *p*-toluenesulfonic acid (9.5 mg, 0.05 mmol) in DMF (1 mL), AcOH (3.0 mg, 0.05 mmol) in DMF (1 mL),

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NH_4Cl (2.7 mg, 0.05 mmol) in DMF (1 mL), K_2CO_3 (35 mg, 0.25 mmol) in DMF (0.5 mL) and water (0.5 mL), or aqueous NH_3 (12.4 M, 0.2 mL) mixed with DMF (0.8 mL). The vial was flushed with argon, sealed with a cap, and left to react in a microwave reactor for 30 min at 150 °C. The results are shown in Table 1.

Effect of Additives in Flow Experiments. The system was configured as shown in Scheme 2. The additive (*p*-toluenesulfonic acid, AcOH, NH_4Cl, K_2CO_3 (aq) or NH_3 (aq), see Table 1) was dissolved in DMF and pumped through a high temperature stainless steel reactor (flow rate: 0.500 mL/min, volume: 10 mL, residence time: 20 min, temperature: 240 °C). The stream from the first reactor was mixed with a stream of 2-chloro-3-nitropyridine in DMF (1.043 mL, 1.0 mmol, 1.0 M, flow rate: 0.500 mL/min) and the mixture was passed through a second reactor (volume: 10 mL, residence time: 10 min, temperature: 50 °C) followed by a back pressure regulator (25 bar). The results are shown in Table 1.

Effect of Temperature. The system was configured as shown in Scheme 1. 2-Chloro-3-nitropyridine (1.585 g, 10.00 mmol) was dissolved in DMF (10.0 mL) and NH_3 (aq, 12.4 M, 2.0 mL) was dissolved in DMF (8.0 mL). 1.043 mL of each solution were pumped through separate pumps at 0.167 mL/min each (total flow rate: 0.333 mL/min), mixed in a T-piece and passed through a high temperature stainless steel reactor (10 mL; temperature: 150, 200, or 250 °C; residence time: 30 min) followed by a back pressure regulator (25 bar). The results are presented in Table 2.

General Method A. A solution of the electrophile (3.0 mL, 0.50 or 1.00 M in DMF) was loaded into a sample loop (1.043 mL). The solution was injected into a DMF stream pumped at 0.167 mL/min and mixed with a stream of aqueous NH_3/DMF (12.4 M of aqueous NH_3 mixed with DMF (1:9); flow rate: 0.167 mL/min). The mixture was passed through a high temperature stainless steel reactor (10 mL, 240 °C, residence time: 30 min) followed by a cooling element (1 m) and a back pressure regulator (25 bar). Unless otherwise stated, the collected product was diluted with brine (100 mL) and the product was extracted with EtOAc (3 × 100 mL). The combined organic phases were then dried over $MgSO_4$ and concentrated, and the residue was purified by column chromatography (CombiFlash Rf, 24 g silica, eluent: heptane/EtOAc).

General Method B. Aqueous NH_3/DMF (12.4 M aqueous NH_3 mixed with DMF (1:9)) was pumped (0.250 mL/min) through a stainless steel reactor (10 mL, 240 °C, residence time: 40 min) followed by a cooling element (1 m). A solution of the electrophile (3.0 mL, 0.25 or 0.50 M in DMF) was loaded into a sample loop (1.043 mL). The solution was injected into a DMF stream (0.250 mL/min) and mixed with the aqueous NH_3/DMF stream exiting the stainless steel reactor. The mixture was passed through a PFA reactor (10 mL, 30 or 50 °C, residence time: 20 min) followed by a back pressure regulator (25 bar). Unless otherwise stated, the collected product was diluted with brine (100 mL) and the product extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated, and the residue was purified by column chromatography (CombiFlash Rf, 24 g silica, eluent: heptane/EtOAc).

***N*,*N*-Dimethyl-3-nitropyridin-2-amine (Table 3, Entry 1).** The title compound was prepared from 2-chloro-3-nitropyridine (475.6 mg, 3.000 mmol) according to method A. The collected solution was diluted with EtOAc (100 mL), washed with water (3 × 200 mL), dried over $MgSO_4$, and filtered and the solvent evaporated. The product was purified by column chromatography (CombiFlash Rf, 24 g silica, eluent: pentane/EtOAc). The solvent was evaporated by heating the eluted solution to 90 °C (ambient pressure) to yield 102.2 mg (59%) of the title compound. NMR data agree with those of Kodimuthali et al.[2d] and Rasala et al.[8]

***N*,*N*-Dimethylpyridin-4-amine (Table 3, Entry 2).** The title compound was prepared from 4-chloropyridine hydrochloride (225.1 mg, 1.500 mmol) according to method A. The collected solution was diluted with brine (100 mL), extracted with EtOAc (3 × 100 mL), dried over $MgSO_4$, and filtered and the solvent evaporated to afford 49.4 mg (78%) of the title compound: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, J = 5.8 Hz, 2H), 6.49 (d, J = 6.5 Hz, 2H), 3.00 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 149.2, 106.7, 39.2. ^{1}H NMR data agree with those of Kodimuthali et al.[2d]

***N*^{4},*N*^{4},6-Trimethylpyrimidine-2,4-diamine (Table 3, Entries 3 and 4).** The title compound was prepared from 2-amino-4-chloro-6-methylpyrimidine (222.0 mg, 1.546 mmol) according to method A. The collected product was diluted with saturated aqueous K_2CO_3 (100 mL) and extracted with EtOAc (3 × 100 mL). The organic phases were collected, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography: A 24 g silica column was flushed with 10% triethylamine in EtOAc and washed with EtOAc before the chromatography. Eluent EtOAc/2% triethylamine in EtOAc: yield 60.4 mg (74%); white crystalline solid; mp 159−168 °C dec; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.99 (s, 2H), 2.98 (s, 6H), 2.16 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 163.7, 162.3, 92.6, 37.0, 23.8; HRMS calcd for $C_7H_{13}N_4$ (M + H) 153.1135, found 153.1137. Attempted preparation of the title compound from 2-amino-4-chloro-6-methylpyrimidine (222.3 mg, 1.548 mmol) according to method B was unsuccessful, and no product or remaining starting material could be identified by LC−MS analysis of the reaction mixture.

Scale-up. 2-Amino-4-chloro-6-methylpyrimidine (10.36 g, 72.2 mmol) was dissolved in DMF to a total volume of 140 mL. This solution (135 mL) and a solution of aqueous NH_3/DMF (12.4 M aqueous NH_3 mixed with DMF (1:9)) were pumped via separate pumps (flow rate of each pump: 0.167 mL/min). The streams were mixed in a T-piece and continued through a high-temperature stainless steel reactor (10 mL, 240 °C, residence time: 30 min) followed by a cooling element (1 m) and a back-pressure regulator (25 bar). The collected product was diluted with saturated aqueous K_2CO_3 (500 mL) and extracted with EtOAc (3 × 500 mL). The organic phases were collected, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (220 g silica flushed with 10% triethylamine in EtOAc and washed with EtOAc; eluent, EtOAc/2% triethylamine in EtOAc): yield 8.78 g (83%).

6-Ethyl-*N*,*N*,2-trimethylquinolin-4-amine (Table 3, Entry 5). The title compound was prepared from 4-chloro-6-ethyl-2-methylquinoline (617.7 mg, 3.003 mmol) according to method A. The collected product was diluted with EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL), and the organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to yield 184.4 mg (82%) of the title compound as a pale yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 0.9 Hz, 1H), 7.45 (dd, J = 8.6, 1.9 Hz, 1H), 6.63 (s, 1H), 2.96 (s, 6H), 2.79 (q, J = 7.6 Hz, 2H), 2.63 (s, 3H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 157.6, 148.3, 140.2, 130.1, 129.2, 122.1, 121.7, 108.5, 44.2, 29.4, 25.8, 16.0; HRMS calcd for $C_{14}H_{19}N_2$ (M + H) 215.1543, found 215.1541.

***N*,*N*-Dimethylquinolin-2-amine (Table 3, Entries 6 and 7).** The title compound was prepared from 2-chloroquinoline (490.7 mg, 2.999 mmol) according to method A. The collected product was diluted with EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL), the organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to yield 160.6 mg (89%) of the title compound. NMR data agrees with Lundgren et al.[9] Alternatively, the title compound was prepared according to method A from 2-bromoquinoline (660.0 mg, 3.172 mmol). The collected product was diluted with EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL), and the organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to yield 146.8 mg (77%) of the title compound.

2-Bromo-*N*,*N*-dimethyl-4-nitroaniline (Table 3, Entry 8). The title compound was prepared from 2-bromo-1-chloro-4-nitrobenzene (708.8 mg, 2.998 mmol) according to method A. The collected product was diluted with EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL), and the organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to yield 222.2 mg (87%) of the title compound: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, J = 2.7 Hz, 1H), 8.06 (dd, J = 9.0, 2.7 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 2.99 (s, 6H); ^{13}C NMR (151

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MHz, $CDCl_3$) δ 157.2, 141.1, 130.4, 123.9, 118.5, 114.5, 43.5. ^{1}H NMR data agree with those of Doyle et al.[10]

***N,N*-Dimethyl-2-nitro-4-(trifluoromethyl)aniline (Table 3, Entries 9 and 10).** The title compound was prepared from 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (627.7 mg, 3.002 mmol) according to method A. The collected product was diluted with EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL), and the organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to yield 191.0 mg (78%) of the title compound as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 1.5 Hz, 1H), 7.57 (dd, J = 9.0, 2.1 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 2.97 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.8 (s), 136.8 (s), 129.6 (q, J = 3.3 Hz), 124.8 (q, J = 12.3 Hz), 123.7 (q, J = 270.8 Hz), 118.4 (q, J = 34.3 Hz), 117.8 (s), 42.1 (s); HRMS calcd for $C_9H_{10}F_3N_2O_2$ (M + H) 235.0689, found 235.0690. Alternatively, the title compound was prepared from 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (315.1 mg, 1.507 mmol) according to method B to yield 96.5 mg (82%).

***N,N*-Dimethyl-1*H*-benzo[*d*]imidazol-2-amine (Table 3, Entry 11).** The title compound was prepared from 2-chloro-1*H*-benzo[*d*]-imidazole (229.0 mg, 1.501 mmol) according to method A. The collected product was diluted with water (100 mL), the product extracted with EtOAc (100 mL), and the organic phase dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to yield 77.4 mg (92%) of the title compound: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.16 (d, J = 7.7 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.84 (t, J = 7.4 Hz, 1H), 3.03 (s, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.9, 143.8, 134.4, 120.2, 118.2, 114.8, 108.7, 38.1. ^{1}H NMR data agree with those of El-Faham et al.[11]

***N,N*-Dimethylbenzo[*d*]thiazol-2-amine (Table 3, Entries 12 and 13).** The title compound was prepared from 2-chlorobenzo[*d*]-thiazole (256.3 mg, 1.511 mmol) according to method A. The collected product was diluted with water (100 mL), the product extracted with EtOAc (100 mL), and the organic phase dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to yield 80.9 mg (86%) of the title compound. NMR data agree with those of Cho et al.[12] Alternatively, the title compound was prepared from 2-bromobenzo[*d*]thiazole (319.4 mg, 1.492 mmol) according to method A to yield 71.8 mg (78%).

4-(Dimethylamino)-3-nitrobenzonitrile (Table 3, Entries 14 and 15). Attempted preparation of the title compound from 4-chloro-3-nitrobenzonitrile (273.6 mg, 1.499 mmol) according to method A afforded a complex mixture; LC−MS showed 14% product and 86% unidentified side products. Alternatively, the title compound was prepared from 4-chloro-3-nitrobenzonitrile (273.5 mg, 1.498 mmol) according to method B to yield 96.3 mg (97%). NMR data agree with those of Brzozowski et al.[13]

2-(Dimethylamino)-4-methylquinoline-3-carbonitrile (Table 3, Entry 16). The title compound was prepared from 2-chloro-4-methylquinoline-3-carbonitrile (304.1 mg, 1.501 mmol) according to method B to yield 75.2 mg (68%).: pale yellow crystalline solid; mp 101−102 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 − 7.76 (m, 1H), 7.71 − 7.68 (m, 1H), 7.61 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.29 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 3.25 (s, 6H), 2.81 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.0, 154.6, 147.9, 132.3, 127.8, 124.3, 123.7, 121.9, 117.7, 97.9, 41.1, 17.7; HRMS calcd for $C_{13}H_{14}N_3$ (M + H) 212.1182, found 212.1176.

Ethyl 4-(Dimethylamino)quinoline-3-carboxylate (Table 3, Entry 17). The title compound was prepared from ethyl 4-chloroquinoline-3-carboxylate (353.7 mg, 1.501 mmol) according to method B but with the temperature of the second reactor increased to 50 °C: yield 101.0 mg (79%); yellow gum; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.07 (dd, J = 8.5, 1.0 Hz, 1H), 7.97 (dd, J = 8.4, 0.8 Hz, 1H), 7.60 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 7.41 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.03 (s, 6H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4, 157.4, 151.2, 150.5, 130.2, 129.9, 125.7, 125.4, 124.9, 116.8, 61.4, 44.2, 14.4; HRMS calcd for $C_{14}H_{17}N_2O_2$ (M + H) 245.1285, found 245.1275.

2-Bromo-*N,N*-dimethyl-4-nitroaniline (Table 3, Entry 18). The title compound was prepared from 2-bromo-1-fluoro-4-nitrobenzene (165.9 mg, 0.754 mmol) according to method B to yield 62.6 mg (97%) without column chromatography: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, J = 2.7 Hz, 1H), 8.08 (dd, J = 9.0, 2.7 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 2.97 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.2, 141.3, 130.4, 123.9, 118.4, 114.7, 43.5; ^{1}H NMR data agrees with those of Doyle et al.[10]

***N,N*-Dimethylbenzo[*d*]oxazol-2-amine (Table 3, Entry 19).** The title compound was prepared from 2-chlorobenzo[*d*]oxazole (230.3 mg, 1.500 mmol) according to method B to yield 79.5 mg (94%) without column chromatography. NMR data agree with those of Cho et al.[12]

4-Chloro-*N,N*-dimethyl-2-nitroaniline (Table 3, Entry 20). The title compound was prepared from 4-chloro-1-fluoro-2-nitrobenzene (132.7 mg, 0.756 mmol) according to method B to yield 41.6 mg (79%). NMR data agree with those of Yang et al.[14]

***N,N,4*-Trimethyl-5-nitropyridin-2-amine (Table 3, Entry 21).** The title compound was prepared from 2-chloro-4-methyl-5-nitropyridine (257.3 mg, 1.491 mmol) according to method B to yield 86.9 mg (92%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.19 (s, 1H), 3.15 (s, 6H), 2.55 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.2, 148.1, 144.8, 135.6, 106.5, 38.3, 22.2; HRMS calcd for $C_8H_{12}N_3O_2$ (M + H) 182.0924, found 182.0926.

5-Bromo-*N,N*-dimethyl-2-nitroaniline (Table 3, Entries 22 and 23). Attempted preparation from 4-bromo-2-fluoro-1-nitrobenzene (335.2 mg, 1.524 mmol) according to method A was unsuccessful, and no product or starting material was observed by LC−MS. Instead, the title compound was prepared from 4-bromo-2-fluoro-1-nitrobenzene (330.3 mg, 1.501 mmol) according to method B but with the flow rate of each pump increased to 0.500 mL/min to yield 125.8 mg (97%) without column chromatography: yellow crystalline solid; mp 47−49 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 6.88 (dd, J = 8.7, 2.0 Hz, 1H), 2.87 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.9, 137.5, 128.2, 128.0, 120.8, 120.5, 42.4; HRMS calcd for $C_8H_{10}BrN_2O_2$ (M + H) 244.9920, found 244.9912.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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