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An Improved Synthesis of 6-Chloro-5-methylpyridin-2-amine: A Key Intermediate for Making Lumacaftor

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Abstract

A safe and efficient synthesis of 6-chloro-5-methylpyridin-2-amine, a key intermediate for lumacaftor, is described, which avoids the utilization of peroxide. In this four-step sequence, starting from 2-amino-6-chloropyridine, the crucial 5-position methylation was achieved via a Suzuki-Miyaura cross-coupling reaction. By adopting this synthetic route, 6-chloro-5-methylpyridin-2-amine was produced on a hectogram scale with 62.4% overall yield and 99.49% purity.

Key words： 6-chloro-5-methylpyridin-2-amine, lumacaftor, methylation, safe

INTRODUCTION

Lumacaftor (**1**, Figure 1) is one of the active ingredients in Orkambi®, which was approved as a fixed dose tablet by FDA and EMA in 2015 for the treatment of cystic fibrosis, a life-threatening genetic disorder.[1-7] 6-Chloro-5-methylpyridin-2-amine **2** is one of the key intermediates of lumacaftor,[8] hence, it is of great significance to develop a reliable and efficient synthetic route for **2**.

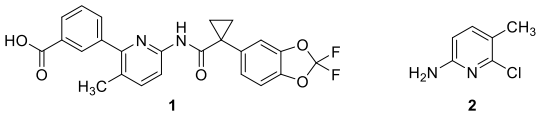


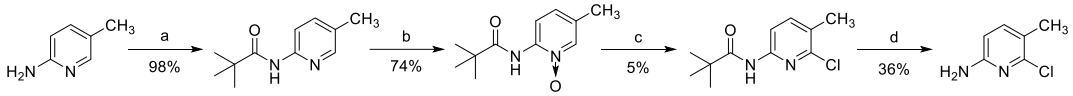
Figure 1. Structures of Lumacaftor **1** and 6-Chloro-5-methylpyridin-2-amine **2**

Several approaches for the synthesis of **2** have been reported.[8-11] Starting from 5-methylpyridin-2-amine **3**, Hadida Ruah et al. reported a four-step linear synthesis of **2** with an overall yield of 1.3% (Scheme 1).[8] The 6-position chlorination was achieved through pyridine *N*-oxide **6** with phosphorus oxychloride. However, considering the factors of safety, facility maintenance, and sewage treatment, the excessively used peroxide and phosphorus oxychloride may not be suitable for industrial production. Bhirud et al. reported another approach for the preparation of **2** beginning with 2-chloro-3-methylpyridine **7** (Scheme 2).[9] The *N*-oxide intermediate **8** was activated with trifluoroacetic anhydride in acetonitrile, and followed by reaction with ethanolamine, afforded **2** in 37.3% overall yield. In our previous work, by referring to relevant literature, [10-13] we developed a synthetic route that has already been applied to production (Scheme 3). However, apart from the issues of harsh conditions and low yield, the introduction of the amino group required the utilization of the big fragment **11**, which may bring concerns to atom economy and waste disposal.

Among the previously synthetic routes showed above, the preparation of **2** inevitably relied on the

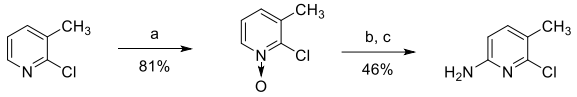
key pyridine *N*-oxide intermediates to achieve subsequent *ortho*-position chlorination or amination. However, peroxide and phosphorus oxychloride used in these low-yielding routes may cause safety and environmental issues. Herein, we report an entirely different synthetic approach, which provided **2** with high quality while circumventing issues associated with previous routes.

Scheme 1. Hadida Ruah's Approach for the Synthesis of 2



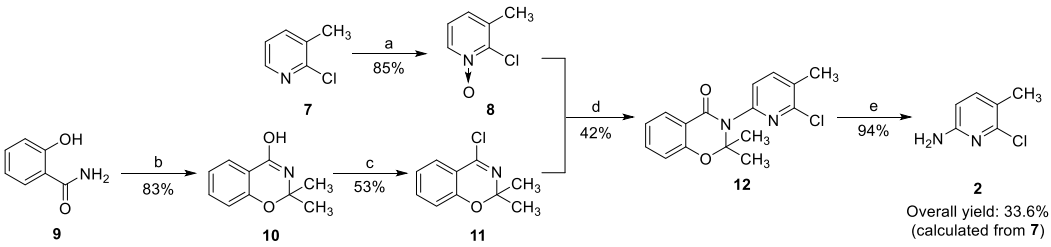
Reagents and conditions:a) pivaloyl chloride (1.2 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C - rt; b) 30% H_2O_2, AcOH, 80 °C; c) $POCl_3$ (4.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 50 °C; d) 6M HCl, 80 °C.

Scheme 2. Bhirud's Approach for the Synthesis of 2



Reagents and conditions:a) mCPBA (2.0 equiv), CH_2Cl_2, rt; b) trifluoroacetic anhydride (1.5 equiv), pyridine (3.9 equiv), MeCN, 65-70 °C; c) Ethanolamine,10-15 °C, rt.

Scheme 3. Our Previous Work for the Synthesis of 2



Reagents and conditions:a) *o*-phthalic anhydride (3.0 equiv), 30% H_2O_2 (3.0 equiv), CH_2Cl_2, reflux; b) 2,2-dimethoxypropane (2.5 equiv), p-toluenesulfonic acid (0.1 equiv), acetone, reflux; c) $POCl_3$ (10.0 equiv), 60 °C; d) **8** (1.0 equiv), **11** (2.0 equiv), 1,2-dichloroethane, reflux; e) conc. HCl (40.0 equiv), reflux.

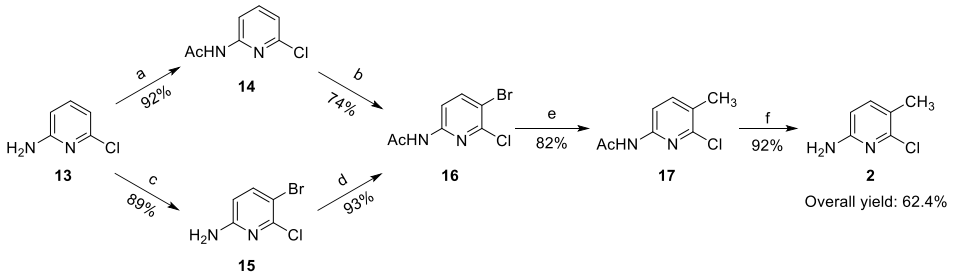
RESULTS AND DISCUSSION

Since the major issues in previous approaches were the introduction of amine or chlorine, which required harsh conditions and gave low yields, hence, we explored the idea to design a route that started with a raw material, which already included the amine and the chlorine in the proper positions. After our evaluation, the commercially available 2-amino-6-chloropyridine **13** was considered as the optimal choice, which could be easily converted from the low-cost 2,6-dichloropyridine via direct ammonolysis[14, 15] or a hydrazinolysis-reduction sequence.[16] Therefore, the synthetic problem was reduced to the regioselective introduction of the 5-methyl group, which we envisioned could be accomplished by stepwise construction of intermediate **16** followed by a Suzuki-Miyaura cross-coupling reaction (Scheme 4).

In our initial efforts, **16** was prepared from the *N*-acetylation of **13** and the subsequent bromination of **14**. The *N*-acetylation was easy to occur, but the downstream bromination was plagued by the low conversion of **14** and excessive consumption of *N*-bromosuccinimide (NBS, 2.0 equiv), providing **16** in a two-step yield of 68.1%. In further trials, the order of acetylation and bromination reactions was reversed, which proved to be a better approach. Compound **13** was amenable to be directly brominated with equimolar NBS at 0-5 °C,[17, 18] affording the selectively mono-brominated product **15** in 89% yield, probably due to the increased electron density in 5-position of **13** in

comparison with that in **14**. Afterwards, the mono-brominated product **15** was acetylated to produce **16** in an improved two-step yield of 82.8% after simple purification. In both methods, the bromination reactions were performed in acetonitrile due to the good compatibility between NBS and acetonitrile.[19]

Scheme 4. Improved Synthetic Route for 2

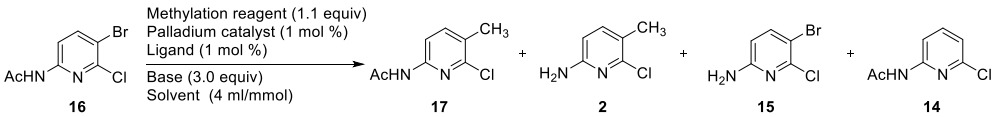


Reagents and conditions: a) acetyl chloride (1.1 equiv), pyridine (2.0 equiv), CH_2Cl_2, 0-5 °C; b) NBS (2 equiv), MeCN, reflux; c) NBS (1.0 equiv), MeCN, 0-5 °C; d) acetyl chloride (1.1 equiv), pyridine (2.0 equiv), CH_2Cl_2, 0-5 °C; e) methylboronic acid (1.1 equiv), $Pd(OAc)_2$ (1 mol %), DPEphos (1 mol %), $NaHCO_3$ (3.0 equiv), 1,2-dimethoxyethane/H_2O (1:1 mixture), reflux; f) conc. HCl (3.0 equiv), MeOH, 50 °C.

When the necessary precursor **16** had been established, the subsequent 5-position methylation was carried out via a Suzuki-Miyaura cross-coupling reaction.[20, 21] Since the methylation procedure was the critical step in our route, the optimization of methylation reagents, solvents, catalysts, ligands, and bases was undertaken.

Initially, three commercially available methylating agents were investigated (Table 1). All of them achieved complete conversion of **16**, with the HPLC area of **17** ranging from 87.1% to 90.2%. Nevertheless, nearly 10% of deacylated product **2** was detected in all three reactions. Although **2** is the target product, it would complicate both quality control and purification. Two other byproducts which were formed were the deacylated impurity **15** (0.1-0.2%) and debrominated impurity **14** (1.1-1.5%). When the methylboronic acid was utilized (Table 1, entry 3), a slight increase of **17,** along with a tiny decrease of **2** were detected. Moreover, in terms of cost and commercial availability, methylboronic acid displayed obvious merits over methyl boronic acid pinacol ester and potassium methyltrifluoroborate. Considering the advantages showed above, methylboronic acid was regarded as the best choice.

Table1. Optimization of Methylation Reagents for the Methylation Step[a]



Entry	Methylation reagent	Conversion (%)[b]	HPLC purity in reaction mixture (%)[c]			
			17	**2**	**15**	**14**
1	Potassium methyltrifluoroborate	100	87.1	11.2	0.2	1.5
2	Methyl boronic acid pinacol ester	100	88.5	10.3	0.1	1.1
3	Methylboronic acid	100	90.2	8.5	0.2	1.1

[a] Reagents and conditions: **16** (1 mmol), methylation reagent (1.1 mmol), $Pd(dppf)Cl_2$ (1 mol %), Na_2CO_3 (3 mmol), 4 ml of dioxane/H_2O (1:1 mixture), reflux. The reaction was stirred for 10 hours and monitored by TLC prior to HPLC analysis. [b] Conversion (%) = 100 - HPLC area (%) of **16** at 250 nm. [c]Calculated from the HPLC area (%) at 250 nm.

As is shown in Table 2, the influence of solvents was enormous on both conversion rate and impurity control. The conversion rates in biphasic systems (Table 2, entries 5–8) were generally much higher than that in homogeneous ones (Table 2, entries 1–4), probably due to biphasic solvents were able to promote the dissolution and contact of substrates, bases and catalysts. When it comes to the

level of the product **17,** as well as impurity control of **2**, **14**, **15**, an obvious improvement was observed using 1,2-dimethoxyethane/H_2O system (Table 2, entry 8) in comparison with the results of toluene/H_2O, EtOH/H_2O, and 1,4-dioxane/H_2O (Table 2, entry 5–7). Hence, 1,2-dimethoxyethane/H_2O was selected as the optimal solvent system.

Table2. Optimization of Solvents for the Methylation Step[a]

Entry	Solvent	Conversion (%)[c]	HPLC purity in reaction mixture (%)[d]			
			17	**2**	**15**	**14**
1	Toluene	1.5	1.4	<0.1	0	0.1
2	1,4-Dioxane	5.2	4.7	<0.1	<0.1	0.3
3	1,2-Dimethoxyethane	4.8	4.7	<0.1	0	<0.1
4	EtOH	13.7	13.4	0	0.1	0.2
5	Toluene/H_2O[b]	64.2	54.7	1.0	5.4	3.1
6	EtOH/H_2O[b]	100	70.5	10.8	0	18.7
7	1,4-Dioxane/H_2O[b]	100	90.2	8.5	0.2	1.1
8	1,2-Dimethoxyethane/H_2O[b]	99.9	94.3	4.4	0.1	1.1

[a] Reagents and conditions: **16** (1 mmol), methylboronic acid (1.1 mmol), Pd(dppf)Cl_2 (1 mol %), Na_2CO_3 (3 mmol), 4 ml of solvents, reflux. The reaction was stirred for 10 hours and monitored by TLC prior to HPLC analysis. [b] 4 ml of mixed solvents (1:1 mixture). [c] Conversion (%) = 100 - HPLC area (%) of **16** at 250 nm. [d]Calculated from the HPLC area (%) at 250 nm.

Since impurities **2** and **15** are likely to be hydrolyzed from **17** and **16**, respectively, the effect of the base on the methylation step was then studied (Table 3). High conversion rate of **16** was obtained in the presence of all four different bases, while an obvious improvement of **17** and a visual reduction of **2** were detected along with the decrease of alkalinity. When the sodium bicarbonate was used (Table 3, entry 4), the levels of the target product **17**, impurity **2**, and impurity **14** were acceptable, while impurity **15** was barely exist. Therefore, sodium bicarbonate was chosen as the base in the following research.

Table3. Optimization of Bases for the Methylation Step[a]

Entry	Base	Conversion (%)[b]	HPLC purity in reaction mixture (%)[c]			
			17	**2**	**15**	**14**
1	Cs_2CO_3	99.8	85.5	13.1	0.2	1.0
2	K_3PO_4	99.9	92.4	5.6	<0.1	1.8
3	Na_2CO_3	99.9	94.3	4.4	0.1	1.1
4	$NaHCO_3$	99.9	97.7	1.1	<0.1	1.1

[a]Reagents and conditions: **16** (1 mmol), methylboronic acid (1.1 mmol), Pd(dppf)Cl_2 (1 mol %), base (3 mmol), 4 ml of 1,2-dimethoxyethane /H_2O (1:1 mixture), reflux. The reaction was stirred for 10 hours and monitored by TLC prior to HPLC analysis. [b]Conversion (%) = 100 - HPLC area (%) of **16** at 250 nm. [c]Calculated from the HPLC area (%) at 250 nm.

Subsequently, a series of commonly used palladium catalysts and ligands were employed in the methylation step. Compared with the other two palladium catalysts, $Pd(OAc)_2$ displayed slight advantages in both conversion rate improvement and impurity control (Table 4, entries 1–3). The influence of ligands was also investigated (Table 4, entries 3–7), and the results showed that the level of **17** was able to achieve 98.8% by utilizing the combination of $Pd(OAc)_2$ and DPEphos (entry 7), while all single impurities were controlled within 0.6%, indicating the catalytic system of $Pd(OAc)_2$/DPEphos was the optimum selection among all the conditions.

Table4. Optimization of Catalysts and Ligands for the Methylation Step[a]

Entry	Catalyst	Ligand	Conversion (%)[c]	HPLC purity in reaction mixture (%)[d]			
				17	**2**	**15**	**14**
1	$Pd_2(dba)_3$	dppf	96.7	96.1	0.4	0	0.2
2	$Pd(dppf)Cl_2$	---[b]	99.9	97.7	1.1	<0.1	1.1
3	$Pd(OAc)_2$	dppf	100	98.1	1.1	0	0.8
4	$Pd(OAc)_2$	PPh_3	73.0	72.2	0.4	0	0.4
5	$Pd(OAc)_2$	BINAP	90.0	89.1	0.5	0	0.4
6	$Pd(OAc)_2$	Xantphos	94.5	93.5	0.5	0	0.5
7	$Pd(OAc)_2$	DPEphos	100	98.8	0.6	<0.1	0.5

[a] Reagents and conditions: **16** (1 mmol), methylboronic acid (1.1 mmol), catalyst (1 mol %), ligand (1 mol %), $NaHCO_3$ (3 mmol), 4 ml of 1,2-dimethoxyethane /H_2O (1:1 mixture), reflux. The reaction was stirred for 10 hours and monitored by TLC prior to HPLC analysis. [b]Not additionally added. [c]Conversion (%) = 100 - HPLC area (%) of **16** at 250 nm. [d]Calculated from the HPLC area (%) at 250 nm.

After preliminary optimization of reaction conditions, the methylation step was scaled to more than 300 g by utilizing the conditions of entry 7 in Table 4, providing **17** in a yield of 82% after simple purification procedure. With the key intermediate **17** in hand, deacetylation under acidic condition was straightforward, offering 130 g of high purity **2** in an overall yield of 62.4%.

CONCLUSION

In conclusion, starting from commercially available **13**, an improved four-step synthetic route was developed for the synthesis of **2**, while the use of peroxide and phosphorus oxychloride was averted. By utilizing this approach, **2** was obtained on a hectogram scale with decent overall yield (62.4%) and high quality (99.49% by HPLC), which made this approach environmentally friendly, safe, and feasible for commercial application.

EXPERIMENTAL SECTION

General procedures: All commercially available chemicals and solvents were directly used without further purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (GF-254). High-resolution mass spectra (HRMS) were measured on an Agilent 1290-6545 UHPLC-QTOF LC/MS spectrometer. ^{1}H NMR and $^{13}C\{^1H\}$ NMR data were recorded on a Brucker 500 Hz instrument using TMS as internal standard. Multiplicities were denoted as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad.

***N*-(6-Chloropyridin-2-yl)acetamide (14).** To a 1 L flask were charged 2-amino-6-chloropyridine (50 g, 388.9 mmol), pyridine (61.5 g, 777.8 mmol), and CH_2Cl_2 (300 mL), then acetyl chloride (33.6 g, 427.8 mmol, diluted with 100 ml of CH_2Cl_2) was added dropwise over a period of 20 min at 0-5 °C under ice bath. The reaction mixture was stirred for an additional 1 h, and it was successively washed with 2M HCl (175 mL) and brine (300 mL), then the organic layer was dried with Na_2SO_4. The solvent was removed by rotary evaporation, and the resulting solid was slurried with n-heptane (300 mL), affording **14** (61.0 g, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.99, 151.32, 148.91, 141.14, 119.76, 112.18, 24.74. HRMS (ESI-QTOF): *m/z* Calcd for $C_7H_7BrClN_2O$ $[M + H]^+$: 171.0320; found: 171.0316. Melting point 146-148 °C.

5-Bromo-6-chloropyridin-2-amine (15). 2-Amino-6-chloropyridine (200 g, 1.56 mol) was added to a 5 L flask containing acetonitrile (2 L), and cooled to 0-5 °C under ice bath. NBS (277.6 g, 1.56 mol) was then slowly added to the solution over a period of 1 h, and stirred the mixture at 0-5 °C for 4 h, then removed 1 L of acetonitrile by rotary evaporation. To the remaining solution, 2 L of water was added, and the mixture was stirred for 1 h. The resulting precipitate was collected by filtration, and the filter cake was dried in vacuum at 50 °C to afford **15** (287.4 g, 89%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.5 Hz, 1H), 6.33 (d, *J* = 8.5 Hz, 1H), 4.60 (br, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.08, 148.30, 143.40, 108.52, 106.20. HRMS (ESI-QTOF): *m/z* Calcd for $C_5H_5BrClN_2$ $[M + H]^+$: 206.9319; found: 206.9321. Melting point 150-151 °C.

***N*-(5-Bromo-6-chloropyridin-2-yl)acetamide (16).** Acetyl chloride (119.3 g, 1.52 mol) was diluted with CH_2Cl_2 (500 mL), and it was added dropwise to a solution of **15** (286.3 g, 1.38 mol) and pyridine (218.3 g, 2.76 mol) in CH_2Cl_2 (1.5 L) at 0-5 °C over a period of 40 min. The reaction mixture was then stirred for an additional 2 h at room temperature (25 °C). Added 630 mL of 2M HCl to the solution, then the organic layer was washed with 500 mL of water, and concentrated by rotary evaporation. Added 1 L of n-heptane to the mixture, then the precipitate was filtered and dried in vacuum at 50 °C, providing **16** (319.1 g, 93%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.90, 149.86, 148.10, 144.33, 113.58, 113.51, 24.79. HRMS (ESI-QTOF): *m/z* Calcd for $C_7H_7BrClN_2O$ $[M + H]^+$: 248.9425; found: 248.9426. Melting point 166-168 °C.

***N*-(6-Chloro-5-methylpyridin-2-yl)acetamide (17). 16** (317.0 g, 1.27 mol) and methylboronic acid (83.8 g, 1.40 mol) were added to a flask containing $NaHCO_3$ (320.1 g, 3.81 mol), $Pd(OAc)_2$ (2.9 g, 12.7 mmol), and DPEphos (6.8 g, 12.7 mmol). A mixture of 1,2-dimethoxyethane (1.5 L) and H_2O (1.5 L) were then added. After purging the heterogeneous mixture with nitrogen for 10 min, the solution was heated to reflux for 10 h under an inert atmosphere of nitrogen. To the hot mixture was added 30 g activated carbon, and the reaction was cooled to room temperature. The insoluble substances were filtered, then the solution was concentrated to about 1 L. Added 2 L of CH_2Cl_2 to the mixture, and the organic phase was washed with water. Removed the solvent, and added isopropanol (500 mL) to the residue and stirred for 2 h. The resulting precipitate was collected by filtration, and the filter cake was dried in vacuum at 50 °C, producing **17** (191.8 g, 82%) as a light-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 2.31 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.82, 149.10, 148.49, 141.81, 127.79, 112.51, 24.70, 18.85. HRMS (ESI-QTOF): *m/z* Calcd for $C_8H_{10}ClN_2O$ $[M + H]^+$: 185.0476; found: 185.0475. Melting point 151-153 °C.

6-Chloro-5-methylpyridin-2-amine (2). 17 (184.6 g, 1.0 mol) was dissolved in methanol (1.1 L), then concentrated hydrochloric acid (250 mL) was added dropwise to the solution. After stirring the reaction mixture at 50 °C for 3-4 h, the solvent was removed under reduced pressure. Ethyl acetate (1 L) was added to the residue, while saturated sodium carbonate solution was used to regulate the pH of the mixture to 9-10. The organic layer was separated and concentrated, and a mixture of methanol (600 mL) and water (1.2 L) was then added to the residue. The precipitate was filtered and dried in vacuum at 50 °C, affording **2** (130.8 g, 92%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.2

Hz, 1H), 6.35 (d, J = 8.2 Hz, 1H), 4.54 (br, 2H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.63, 148.68, 141.36, 120.56, 107.15, 18.40. HRMS (ESI-QTOF): *m/z* Calcd for $C_6H_8ClN_2$ $[M + H]^+$: 143.0371; found: 143.0367. The ^{1}H NMR and ^{13}C data are consistent with the literature.[11] Melting point 88-90 °C.

ASSOCIATED CONTENT

Supporting Information

NMR spectra for compounds **14**, **15**, **16**, **17**, and **2**.

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Notes

The authors declare no competing financial interest.

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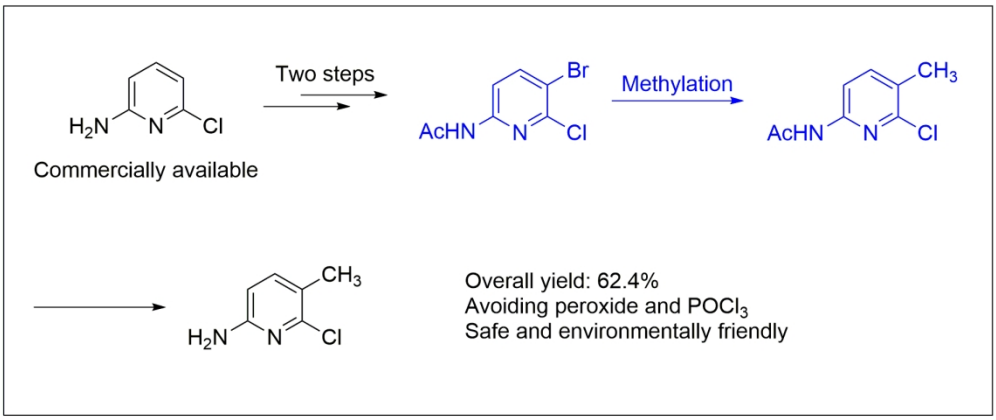

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