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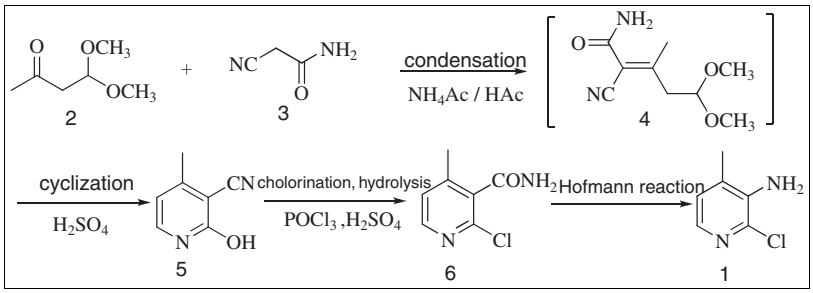

2-Chloro-3-amino-4-methylpyridine (**1**), a key intermediate in the synthesis of nervirapine, was prepared from 2-cyanoacetamide and 4,4-dimethoxyl-2-butanone *via* condensation, cyclization, one-pot reaction of chlorination and hydrolysis, and Hofmann reaction. Utilization of the quadratic orthogonal test resulted in a high yield (62.1%) of the whole process.

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INTRODUCTION

2-Chloro-3-amino-4-methylpyridine (**1**) (Chart 1) is an important intermediate in the synthesis of nervirapine, which is a non-nucleosidic reverse transcriptase inhibitor established to be clinically useful in the treatment of infection by HIV-1 [1].

Some substantial processes have been reported for the synthesis of **1**. Chapman [2] and Gupton [3] developed a way starting from 2-chloro-3-nitro-4-methylpyridine, which was reduced by $SnCl_4$/HCl to generate **1** (Scheme 1). More recently, Hargrave [4], 5] developed another way starting from 2-hydroxy-3-nitro-4-methylpyridine, which underwent chlorination with PCl_5/$POCl_3$ and reduction with $SnCl_4$/HCl (Scheme 2). Both of the two routes have brief reaction steps but suffer from expensive material and regents, so they are unsuitable for the industrial process.

For another route, Knoevenagel condensation of 4,4-dimethoxyl-2-butanone (**2**) with malononitrile followed by cyclization, chlorination, hydrolysis, and Hofmann degradation gave 52.1% yield of the product **1** (Scheme 3) [6]. However, expensive malononitrile, long reaction time (24 h) in the Knoevenagel condensation, excessive stoichiometric PCl_5 in the cyclization, and the contaminate Br_2 in Hofmann reaction limit its application.

A new route proposed in this article is to synthesize **1** from 2-cyanoacetamide (**3**) and 4, 4-dimethoxyl-2-butanone (**2**) (Scheme 4), which was characterized by higher yield, brief steps and less "pollution." We successfully developed an efficient synthesis of **5**; the following chlorination and hydrolysis were carried out in one pot. Br_2 was replaced with sodium hypochlorite in the Hofmann reaction.

RESULTS AND DISCUSSION

Synthesis of 2-hydroxy-3-cyano-4-methylpyridine (5). Synthesis of **5** *via* Knoevenagel condensation was usually performed with a variety of amines and urea as catalyst in the literature [15]. Our efforts focused on the selection of the catalyst. Reaction results with various bases as catalyst were shown in Table 1. Ammonium acetate (4.0 wt %) gave the highest yield (82.1%). On the other hand, the base, sodium methoxide was very strong to generate the isomer of **5**. According to Dawadi [7], both the ammonium acetate and **3** could completely dissolve in acetic acid, achieving a homogeneous system. Therefore, 4.0 wt % of ammonium acetate, as well as 30 wt % of acetic acid, was adopted.

Synthesis of 2-chloro-3-formyl amino-4-methylpyridine (6). Compound **6** was obtained by chlorination and hydrolysis of **5** in one-pot way. Influence of different chlorides was studied, as shown in Table 2.

It can be seen that the reaction using PCl_3 gave the lowest yield, probably because the generated phosphate reduced the sulfuric acid to SO_2. Although $SOCl_2$ was superior to PCl_3, it was still inferior because of its toxicity. $POCl_3$ gave the highest yield; meanwhile, the generated phosphate can be solvent for the system. So $POCl_3$ was chosen as chloride source.

A reaction condition optimized by quadratic orthogonal test was given as follow:

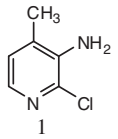
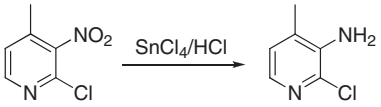
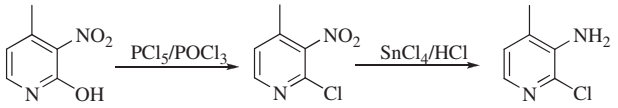


Chart 1. 2-Chloro-3-amino-4-methylpyridine (CAPIC) (**1**).

Scheme 1. Approach to the synthesis of **1**.



Scheme 2. Approach to the synthesis of **1**.



Temperature in hydrolysis (A), the molar ratio of $POCl_3$ to **5** (B), the molar ratio of concentrated sulfuric acid to **5** (C). Number of experiments the second level $m_c = 2^3 = 8$. Zero number of experiments $m_0 = 2$ and the asterisk arm length, $r = \sqrt{\frac{\sqrt{(m_c+2m+m_0)m_c}-m_c}{2}} = 1.287$. Only the variables A and C were explored in 16 sets of experiments (Tables 3 and 4).

The yield and the variables A–C were multivariate-correlated using the polynomial regression method to obtain a regression model as given in Eq. (1).

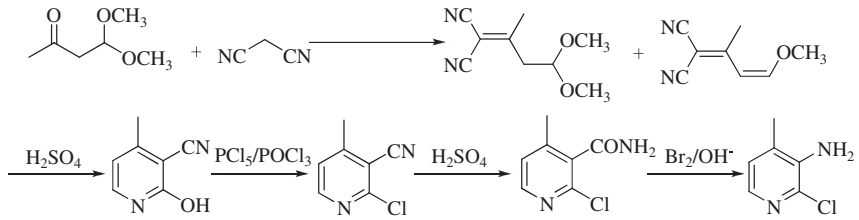
$$y = -227.344B^2 - 3.78C^2 - 0.061A^2 + 564.6881B + 27.557C + 8.1513A - 583.6 \quad (1)$$

By taking $\frac{\partial y}{\partial A} = 0, \frac{\partial y}{\partial B} = 0, \frac{\partial y}{\partial C} = 0,$ the temperature of hydrolysis of 66.8°C, molar ratio of $POCl_3$ to **5** of 1.24, molar ratio of sulfuric acid to **5** of 2.22 were optimized, and the yield of 89.6% was expected.

Synthesis of 2-chloro-3-amido-4-methylpyridine (1). Synthesis of nitrene was the key step in this route. Orthogonal method was used to optimize the reaction condition. The following factors were ought to be considered: the molar ratio of NaClO and **6** (A), the molar ratio of NaOH and **6** (B), reaction temperature (C), reaction time (D). The results were shown in the Tables 5–7.

According to the calculated results, factor A had the largest R value, meaning that the amount of NaClO had

Scheme 3. Approach to the synthesis of **1**.



Scheme 4. Improved synthesis of **1**.

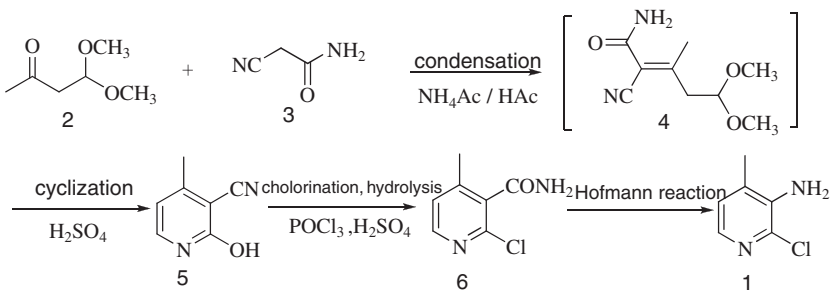


Table 1

Screening of catalysts for synthesis of **5**.

No.	Catalysts	Amount of catalyst/amount of raw material (wt %)	Amount of HAc (wt %)	Yield **5** (%)
1	Sodium methoxide	4	–	–
2	Ammonium acetate	4	–	33.2
3	Piperidine	4	10	64.7
4	Ammonium acetate	2	25	76.5
5	Ammonium acetate	4	30	82.1
6	Ammonium acetate	7	40	82.0
7	Ammonium acetate	4	40	81.9

Table 2

Synthesis results of **6** using different chloride sources.

No.	Chloride reagent	*T* (°C)	Yield (%)
1	PCl_3	76	55.1
2	$POCl_3$	105	86.2
3	$SOCl_2$	78	68.3

Table 3

Response surface experiment encoding table.

		Levels				
Factors	Code	−1	0	1	−1.287	1.287
T (°C)	A	53.34	65	76.66	50	80
$n(POCl_3)/n$(**5**)	B	1.04	1.2	1.36	1	1.4
n(sulfuric acid)/*n*(**5**)	C	4.55	3	4.55	1	5

dominant effect on the reaction. So the molar ratio of NaClO to **6** of 1.0 and the molar ratio of NaOH to **6** of 3.0, with the reaction time of 60 min at 10°C was chosen as the most suitable condition.

CONCLUSIONS

An industrially applicable route for the synthesis of 2-chloro-3-amino-4-methylpyridine was designed and optimized. Ammonium acetate (4.0 wt %) and acetic acid (30 wt %) were adopted, resulting in a high yield of 82.1%. $POCl_3$ was used in chlorination. Statistical experimental design and multivariate modeling helped increase the yield of 2-chloro-3-amino-4-methylpyridine. A quadratic equation was set up to optimize the condition of the reaction.

EXPERIMENTAL

General methods. Melting points were determined using WRR melting point apparatus. TLC analyses were performed on

Table 4

Experimental conditions with corresponding measured for synthesis of **6**.

	Experimental variables			Yield
Entries	*A*	*B*	*C*	*y* (%)
1	76.66	1.36	4.55	78.3
2	53.34	1.36	4.55	72.7
3	76.66	1.36	1.45	63.7
4	53.34	1.36	1.45	55.9
5	76.66	1.04	4.55	69.4
6	53.34	1.04	4.55	63.1
7	76.66	1.04	1.45	57.2
8	53.34	1.04	1.45	49.9
9	65	1.4	3	80.2
10	65	1	3	77.5
11	65	1.2	5	84.6
12	65	1.2	1	62.3
13	80	1.2	3	75.6
14	50	1.2	3	73.9
15	65	1.2	3	86.2
16	65	1.2	3	85.7

Table 5

Factors and levels of experiment.

Factors levels	A	B	C	D
1	1.0	2.0	5	30
2	1.5	3.0	10	60
3	2.0	4.0	15	90

Table 6

Experimental conditions with corresponding measured for synthesis of **1**.

Entries	A	B	C	D	Yield (%)
1	1.0	2.0	5	30	75.6
2	1.0	3.0	10	60	85.1
3	1.0	4.0	15	90	74.1
4	1.5	2.0	10	90	70.4
5	1.5	3.0	15	30	72.9
6	1.5	4.0	5	60	69.2
7	2.0	2.0	15	60	64.6
8	2.0	3.0	5	90	68.7
9	2.0	4.0	10	30	63.8

Table 7

Result analysis table.

Factors	A	B	C	D
k_1	78.30	70.20	71.17	70.77
k_2	70.83	75.60	73.13	73.00
k_3	65.70	69.03	70.53	71.07
R[a]	12.60	6.57	2.60	2.23

[a] $R = k_{max} - k_{min}$.

glass plate (30 × 100 mm^2). GC analyses were performed on GC Agilent 1790F series. HPLC analyses were executed on HPLC Agilent 1100 series charged with C18 column. NMR spectrums were recorded in DMSO or $CDCl_3$ using Bruker, AV 400, 400 MHz.

Starting materials and reagents were commercially purchased and used without further purification.

Preparation of 2-hydroxy-3-cyano-4-methylpyridine (5). To a 500-mL three-necked flask equipped with a mechanic stirrer, a thermometer, and a water separator, 4,4-dimethoxyl-2-butanone (**2**) (37.0 g, 0.28 mol), 2-cyanoacetamide (**3**) (29.4 g, 0.35 mol), ammonium acetate (1.5 g), acetic acid (11.0 g), and toluene (200.0 g) were added under vigorous stirring. The water produced in the reaction was separated. When this step was finished, the toluene was removed under vacuum at 50°C, and the residual liquid was cooled to room temperature, ethanol (100 g) was added under stirring at 25°C. After that, sulfuric acid (50%, 110 g) was added slowly within 40 min, then heated to 50°C for another 30 min, and khaki crystal was precipitated. The whole process was monitored by TLC. After the final step, the reaction mixture was cooled to 5°C, and water (80 g) was added in 50 min. 2-Hydroxy-3-cyano-4-methylpyridine was thus obtained by filtration and recrystallization in ethanol.

(5) (Chart 2). Khaki solid (30.3 g, 82.1% yield), mp: 234.7–236.1°C (lit. [6] mp: 236.0–238.0°C); ^{1}H-NMR (DMSO, 400 MHz) δ: 2.34 (s, 3H, CH_3), 6.29–6.31 (d, 1H, C CH C, J = 6.8 Hz), 7.64–7.65 (d, 1H, N CH C, J = 6.8 Hz), 12.32 (s, 1H, OH). ^{13}C-NMR (DMSO, 100 MHz). δ: 21.17 (C-1), 103.09 (C-2), 108.092 (C-3), 116.14 (C-4, 140.04 (C-5), 160.68 (C-6), 161.57 (C-7).

Preparation of 2-chloro-3-formyl amino-4-methylpyridine (6). To a 500-mL three-necked flask with a mechanic stirrer, a reflux condenser, and a thermometer, $POCl_3$ (43.7 g, 0.285 mol) was added. Then 2-hydroxy-3-cyano-4-methylpyridine (**5**) (30.3 g, 0.23 mol) was added under stirring in 15 min at 35°C. After that, the reaction mixture was heated to reflux. The chlorination reaction was completed in 2 h. Thereafter, the reaction mixture was cooled to 50°C, and sulfuric acid (82.3 g, 0.84 mol) was added in slowly. After the addition was complete, the mixture was heated to 100–105°C, under stirring for 4 h and cooled to 60°C, and water (82.3 g) was added to the flask. The reaction temperature was kept between 65 and 67°C for another 1.5 h. Then cooling, ammonia aqueous (28%) was added slowly to make pH = 7. Precipitation was generated. The solid was filtered and recrystallized in water to give 2-chloro-3-formyl amino-4-methylpyridine (**6**) (Chart 3) (34.6 g, 88.3% yield) as dust-color solid.

Melting point: 176.5–177.9°C (lit. [6] mp: 178–179°C); ^{1}H-NMR (DMSO, 400 MHz) δ: 2.32 (s, 3H, CH_3), 7.33–7.34 (d, 1H, C CH C, J = 4.4 Hz), 7.83 (s, 1H, NH), 8.08 (s, 1H, NH), 8.27–8.28 (d, 1H, N CH C, J = 4.8 Hz). ^{13}C-NMR (DMSO, 100 MHz). δ: 18.97 (C-1), 125.05 (C-2), 134.34 (C-3), 146.48 (C-4), 147.35 (C-5), 149.05 (C-6), 167.02 (C-7).

Preparation of 2-chloro-3-amido-4-methylpyridine (1). To a 500-mL three-necked flask with a mechanic stirrer, a reflux condenser, and a thermometer, NaOH (15.6 g, 0.39 mol) and water (85 g) were added, stirring until the solid was completely dissolved, and cooled to room temperature. To the flask, NaClO (10%, 96.8 g, 0.13 mol) and ethyl alcohol (80 g)

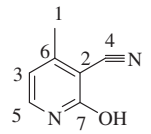


Chart 2. 2-Hydroxy-3-cyano-4-methylpyridine (**5**).

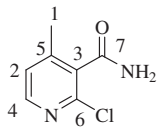


Chart 3. 2-Chloro-3-formyl amino-4-methylpyridine (**6**).

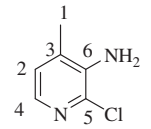


Chart 4. 2-Chloro-3-amido-4-methylpyridine (**1**).

were added to the flask. After cooling to 10°C, 2-chloro-3-formyl amino-4-methylpyridine (**6**) (22 g, 0.13 mol) was added slowly in 10 min. Under stirring for 60 min, then the temperature was increased to 60°C for 3 h. The solvent was removed under vacuum to give crude product. The crude product was cooled to room temperature and filtered, and thus, 2-chloro-3-amido-4-methylpyridine was obtained after recrystallization in toluene.

(1) (Chart 4). White solid (14.7 g, 85.6% yield). mp: 67.4–68.2°C (lit. [6] mp: 69°C); ^{1}H-NMR (DMSO, 400 MHz) 2.16 (s, 3H, CH_3), 5.27 (s. 2H, NH_2), 6.98–6.99 (d, 1H, C CH C, J = 4.8 Hz), 7.51–7.52 (d, 1H, N CH C, J = 4.4 Hz). ^{13}C-NMR (DMSO, 100 MHz). δ: 17.92 (C-1), 125.32 (C-2), 131.93 (C-3), 135.48 (C-4), 136.26 (C-5), 139.91 (C-6).

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