Synthesis of 2-Amino-5-Bromo-3-Iodopyridine

Xiaoyuan Li[1], Xinrui Dong[1], Xueye Shu[1], Yifeng Yu[1], Yingnan Wang[1], Yue Zhang[1,2,3*]

[1.] *School of Chemical and Pharmaceutical Engineering*, Hebei University of Science and Technology, Shijiazhuang, 050018, CHINA;
[2.] Hebei research center of pharmaceutical and chemical engineering, Shijiazhuang, 050018, CHINA;
[3.] State Key Laboratory Breeding Base-Hebei Province Key Laboratory of Molecular Chemistry for Drug, Shijiazhuang, 050018, CHINA;
[*.]Corresponding author: yuezhang@hebust.edu.cn

***Abstract* — 2-Amino-5-Bromo-3-Iodopyridine is an important intermediate of pharmaceuticals and farm chemicals, but there is no detailed research on its synthesis so far including related by-product identification, their reaction conditions and especially factors for scaling up its production. In this paper, 2-amino-5-bromo-3-iodopyridine has been prepared starting from 2-Aminopyridine, involving Bromination with NBS and Iodination with Iodine. The side reaction in Bromination was effectively inhibited due to characterization of the major impurity in 2-amino-3,5-dibromopyridine. Moreover, the feasibility of recycling material in Iodization, which was commercially feasible for the large scale, has been verified. With the established optimal condition, the yield of Bromination was raised to 95.0% and of the Iodization was 73.7%.**

Keywords - 2-Amino-5-bromopyridine, 2-Amino-5-bromo-3-iodopyridine, 2-Amino-3,5-dibromopyridine, Intermediates, Synthesis

I. INTRODUCTION

2-Amino-5-bromo-3-iodopyridine is an important pharmaceutical intermediate having a wide range of applications in pharmaceutical and chemical fields, especially playing an irreplaceable role in the synthesis of tyrosine kinase inhibitor [1,2] which has been widely used for the cancer chemotherapy [3].

Several synthetic routes of 2-amino-5-bromo-3-iodopyridine using 2-aminopyridine as substrate had been reported before and are shown in Fig.(1). [4-9]. The most of the efforts had been concentrated on the yield and selection of reagents. But the problems we must face during scale-up are: (i) cumbersome operations with low product selectivity for (a) [4], (ii) high cost for (b) [4] and (e) [7], (iii) difficult controlling for (c) [4], (iv) long reaction time for (d) [5] and (f) [7,8], (v) troublesome separation process for (g) [9].

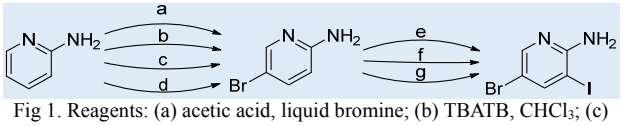

Fig 1. Reagents: (a) acetic acid, liquid bromine; (b) TBATB, $CHCl_3$; (c) $C_{16}H_{37}Br_2N$, $CHCl_3$; (d) acetic anhydride, liquid bromine, H_2O, NaOH; (e) NIS, DMF, TFA; (f) $NaIO_4$, I_2; (g) iodine, benzene sulfonic acid.

The synthetic route, presented in this experiment as shown in Fig.(2)., also started from 2-aminopyridine with successively NBS Bromination and iodination to afford 2-amino-5-bromo-3-iodopyridine [10-12]. Although the adopted synthetic route was changed little in terms of the chemistry, but the reaction conditions and purifying procedures were considerably changed to make the scale-up operation simpler and industrially viable. Three basic improvements exist in (1) the major impurity compound **2** (Fig.2) of the bromination was first separated, characterized as 2-amino-3,5-dibromopyridine; (2) the substrate recycling utilization was realized in iodination; and (3) the simple separating method made the process simply.

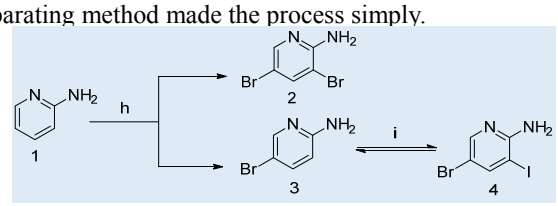

Fig 2. Reagents: (h) NBS, acetone, 10 °C; (i) KI, KIO_3, H_2SO_4, 100 °C.

II. RESULT AND DISSCUSSION

A. Bromination:

The preparation started from 2-aminopyridine, involving brominated by NBS in the presence of acetone as the solvent. The great trouble in this stage is the byproduct always accompanying with the product in a larger quantity resulting the tedious separation process. For controlling the reaction much better, the byproduct was separated and identified first as 2-amino-3,5-dibromopyridine (compound 2). It is elucidated that over-Bromination of the substrate happened in Bromination. Hence, the amount of the brominating agent plays the key role in the yield of the product, and how to inhibit the byproduct emerging becomes important. A series of the experiments were done for looking for an optimal condition not only for the amount of the brominating agent but also involving the other reaction conditions, such as temperature, feeding time of NBS, especially material ratio and the experimental results

are showed in table (1).

The brominated process was initially investigated at relatively low temperature because we hoped the low temperature could prevent formation of dibromo-substituted impurities. But the result shows that the low temperature indeed decrease the content of 2, but it is not an inevitable condition and the effect of the temperature on the content of 2 is irregular (Entry 1-5). Especially, the low temperature means high energy cost for scale-up production. The aim of the research of NBS feeding time was to effectively control the concentration of NBS in the reacting mixture restraining the regional over-bromination. The result shows that the effect of NBS feeding time on the content of 2 is more significant than the temperature, and the batch feeding of NBS brings the better yield than one time joining of NBS with acceptable impurity content (Entry 3 and 6-9). The molar ratio of the substrate and brominating agent has the most significant influence on the yield of 3 and content of 2. Excess NBS could result in over bromination to raise the content of 2 and the equal ratio of the substrate and NBS gives the best yield of the product with the satisfied inhibiting of the impurity (Entry 3 and 10-12).

TABLE **I.** RESEARCH ON THE BROMINATION

Entry	Temperature (ºC)[a]	Ratio[b]	Feeding Time (h)[c]	Yield (%)[d]	Content (%)[e] of **2**
1	-10	1 : 1.05	0.5	85	0.4
2	0	1 : 1.05	0.5	88	1.3
3	10	1 : 1.05	0.5	87	5.9
4	20	1 : 1.05	0.5	89	0.4
5	30	1 : 1.05	0.5	88	1.0
6	10	1 : 1.05	0[f]	75	9.5
7	10	1 : 1.05	1.0	86	9.4
8	10	1 : 1.05	2.0	88	6.2
9	10	1 : 1.05	3.0	91	2.1
10	10	1 : 1.00	0.5	95	0
11	10	1 : 1.10	0.5	57	9.8
12	10	1 : 1.15	0.5	54	13.7

a The thermometer is not calibrated. b Ratio of n (1) : n (NBS). c Time of NBS feeding. d, e Yield and content are calculated from HPLC standard curve method. f Feeding by once time.

B. Iodization:

The iodinated process was not as simple as imagined. Since it was a reversible reaction, the difficulty of this step is not the impurity formation of multi-substituted compounds, like the previous step, but how to make compound **3** into the product in a high conversion rate. The relative research results are shown in table (2). In this process, potassium iodide reacts with potassium iodate under the strong acidic condition to instantly produce iodine which reacts with **3** to afford **4**. Research result of temperature shows that the reaction is incomplete at lower temperature, but the intense sublimation and entrainment of iodine would increase under the reflux system also resulting in the lower yield of **4** (Entry 1-5). Generation and concentration of iodine had a great impact on the iodation of **3** (Fig. 3). The ratio of the amount of potassium iodide and potassium iodate exerted a direct impact on the reaction because it determines the concentration of iodine in the system.

The excess amount of iodide ions may provide enough amount of iodine which is beneficial to the iodation of **3**, but it is also not favorable to the reversible iodation in view of it being a byproduct. In the other hand, iodine ion generated in the iodation may react with iodate to produce iodine. Therefore, to determine a suitable ratio of potassium iodide and potassium iodate is a critical task. As shown in table (2), increase of KI ratio brings an elevatory yield of **4** but the range is rather small when the dosage of KI is over 1.2 equivalents (Entry 2 and 6-9). In the meantime, in view of the sublimation and entrainment of iodine, long period of time maybe result in the decrease of iodinated reagent and is disadvantageous to the reversible reaction (Entry 2 and 10-13).

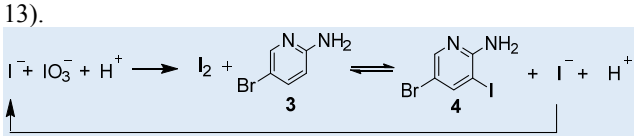

Fig 3. The mechanism of iodization

TABLE II**.** RESEARCH ON THE IODIZATION

Entry	Temperature (°C)[a]	Ratio[b]	Reaction Time (h)	Yield (%)[c]	Content of **3**(%)[d]
1	106[e]	1 : 1.1	1.5	40.2	34.3
2	100	1 : 1.1	1.5	69.4	14.1
3	90	1 : 1.1	1.5	63.4	18.1
4	80	1 : 1.1	1.5	57.9	31.2
5	70	1 : 1.1	1.5	40.7	51.6
6	100	1 : 1.0	1.5	62.3	29.7
7	100	1 : 1.2	1.5	73.7	18.3
8	100	1 : 1.3	1.5	73.9	22.6
9	100	1 : 1.4	1.5	74.0	13.7
10	100	1 : 1.1	0.5	62.3	26.3
11	100	1 : 1.1	1.0	71.2	18.8
12	100	1 : 1.1	2.0	66.4	31.3
13	100	1 : 1.1	2.5	64.6	29.7

a The thermometer is not calibrated. b Ratio: n (KIO3) : n (KI). c, d The total yield and content are calculated from HPLC standard curve method. d Content of unreacted 3. e Reflux temperature.

As shown in table (2), even in the optimal condition, there are 18.3% of **3** left. We found a simple way to separate this part of unconverted material from the product. It was also found that the separated unreacted **3** could be recycled directly for the next batch and the recycled total yield of **4** would be improved about 13.9%.

III. EXPERIMENTAL SETUP

General: Solvents and reagents were commercially available and used without further purification. Acetone, ethanol and ethyl acetate were provided by Tianjin Yongda Chemical Co., Ltd., China. And 2-aminopyridine and NBS were provided by Aladdin Industrial Corporation. The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using an AVANCEDMX-500 (WB) (Bruker, America) at room temperature using TMS as an internal standard and DMSO-d6 or $CDCl_3$ as the solvent. HPLC was performed by using Aligen LC-20AT systems at the wavelength of 245 nm. The column was Hypersil BDS C18 (5 μm, 250×4.6 mm) and the column temperature was 25 °C. The mobile phase was the mixture of acetonitrile/water (40/60, by volume) for 2-amino-5-bromopyridine and (60/40, by volume) for 2-amino-5-bromo-3-iodopyridine at a flow rate of 1.0 $mL \cdot min^{-1}$ and the injection volume was 5 μL.

Preparation of 3: NBS (1.0 g, 5.6 mmol) was added to the mixture of 2-aminopyridine (0.5 g, 5.3 mmol) in acetone (5 mL) dropwise over 0.5 h at 10 °C. The mixture was stirred over 0.5 h. Solvent was removed by evaporation under vacuum and the residue was recrystallized with 90 % ethanol to afford **3** as yellow solid (0.90 g, yield: 95.0%, purity: 97.0%).

Separation of 2: The above recrystallized filtrate was concentrated and purified by column chromatography to afford **2** with petroleum ether/ethyl acetate (10/1, by volume) as mobile phase.

Preparation of 4: A solution of **3** (1.0 g, 5.8 mmol) in 2 mol/L sulfuric acid (10 mL) was stirred and treated portionwise with potassium iodate (0.62 g, 2.9 mmol). The mixture was heated to 100 °C. A solution of potassium iodide (0.57 g, 3.4 mmol) in water (10 mL) was added dropwise over 0.5 h. The mixture was allowed to stir for further 1.5 h then cooled to the ambient temperature. The pH of the aqueous phase was adjusted to 8 by ammonia and the mixture was cooled to 10 °C for 1 h and then filtered. The filter cake was washed with cool water and recrystallized with alcohol (85%) to give **4** (1.27 g, yield: 73.7%, purity: 98.5%).

Recycle of unreacted 3: The above filtrate was extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with distilled water (3×10 mL) and evaporated in vacuum to recover the unreacted **3** as a brown solid (0.23 g, purity: 91.3%). The recovered **3** was reacted as the above step together with 0.79 g 2-amino-5-bromopyridine to give **4** (1.26 g, yield: 73.1%, purity: 98.7%).

IV. ANALYTICAL DATA

2-Amino-5-bromopyridine: ^{1}H NMR (DMSO-d6, 500 Hz), δ: 8.10 (d, 1H), 7.49 (t, 1H), 6.41 (d, 1H), 4.58 (s, 2H); LCMS (ESI) m/z calculated for $C_5H_5N_2Br$ 172.9114, found 172.9000.

2-Amino-3, 5-dibromopyridine: LCMS (ESI) m/z calculated for $C_5H_4N_2Br_2$ 251.8154, found 252.9000.

2-Amino-5-bromo-3-iodopyridine: ^{1}H NMR ($CDCl_3$, 300 MHz,), δ: 8.06 (d, 1H), 7.96 (d, 1H), 5.00 (s, 2H); LCMS (ESI) m/z calculated for $C_5H_4N_2BrI$ 298.8159, found 300.7000.

V. CONCLUSIONS

A convenient and scalable method for preparation of 2-amino-5-bromo-3-iodopyridine has been developed. Total yield of 70% has been achieved from 2-aminopyridine to 2-amino-5-bromo-3-iodopyridine. The optimal condition was with the Bromination for n (2-

aminopyridine) : n (NBS) = 1, the dropping time of NBS solution for 1 h at room temperature, and the iodization for 100 oC, 1.5 h, n (KIO3) : n (KI) =1 : 1.2. The process is convenient and could be easily scaled up. Dibromide product was first separated from the bromination of 2-aminopyridine and identified as 2-amino-3,5-dibromopyridine.

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