

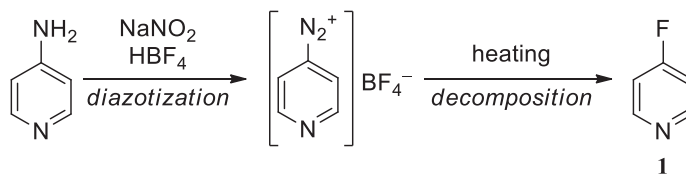
## Detailed experimental procedure for the synthesis of 4-fluoropyridine

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**Abstract.** The Balz-Schiemann reaction of 4-aminopyridine afforded 4-fluoropyridine (**1**) in 20% yield, but the special care was required because **1** was unstable under the aqueous conditions. Both the detailed reaction conditions and the appearance of the reaction mixture are reported in detail. The detailed experimental procedure for the isolation of **1** is also presented. Some comments for  $^1\text{H}$  NMR spectrum of **1** are given.

4-Fluoropyridine (**1**) is an useful reagent especially for the cooperation of 4-pyridyl group through the aromatic nucleophilic substitution.<sup>[1]</sup> The compound **1** is commercially available but expensive, one may plan the synthesis of **1** when he needs **1** in a gram or more quantity.<sup>[2]</sup> In 1958, Wibaut *et al.* reported the first synthesis of **1** by the decomposition of 4-pyridyl diazonium fluoride, generated *in situ* from the 4-aminopyridine with  $\text{NaNO}_2$ , in the aqueous solution of  $\text{HF}$ .<sup>[3]</sup> The best synthetic method for **1** was reported by Suzuki's group,<sup>[4]</sup> anhydrous  $\text{HF}$  was used instead of the aqueous solution of  $\text{HF}$  for the fluorinating reagent. However, the use of  $\text{HF}$  may be avoided if possible because  $\text{HF}$  is well known as a highly toxic substance. Recently, several good synthetic methods for fluoroaryls are explored,<sup>[5]</sup> but the difficulty of the synthesis of **1** is the matter of the purification.

For the author, a chemist of organic synthesis but not used to use  $\text{HF}$ , the Balz-Schiemann reaction of 4-aminopyridine seems to be the most realistic method among the synthetic methods for **1** (Scheme 1); the starting materials are all commercially available and not expensive, and **1** can be obtained in one step. In fact, the author successfully synthesized **1** according to the literatures.<sup>[6]</sup> However, some information about the experimental detail is missed and some modification is made for the isolation of the product. Now the author presents the more detailed experimental procedure of the reaction. The  $^1\text{H}$  NMR spectrum of **1** is also reported.



Scheme 1. Balz-Schiemann reaction for the synthesis of 4-fluoropyridine (**1**).

The difficulty of the synthesis of **1** is due to its instability to water. Hawkins *et al.* observed the formation of the brown solids when the reaction mixture of the product was neutralized.<sup>[7]</sup> They obtained not the desired **1** but *N*-(4'-pyridyl)-4-pyridone. Desai inferred that the brown solids were the polymer material, which formed by polymerization of **1**, and *N*-(4'-pyridyl)-4-pyridone was the product of the hydrolysis of the polymer.<sup>[6b]</sup> From the experimental standpoint, this polymer material is gummy and severely retard the extraction process. So the author modified the extraction process to divide into two parts: the decant and the residual suspension containing brown

solids. By this modification, the extraction process could finish shortly. In order to prevent the further decomposition of the product, the combined organic layer was dried thoroughly with  $\text{CaH}_2$  after the extraction.

The detailed experimental procedure for **1** is as follows: in a round-bottomed, two-necked 200 mL flask equipped with a thermometer and the stirring bar, 42% aqueous solution of  $\text{HBF}_4$  was charged. 4-Aminopyridine (14.4 g, 153 mmol) was added and dissolved by heating to 40 °C with dryer. Then the solution was cooled to 5 ~ 7 °C with the ice-water bath, the fine crystals of 4-pyridylammonium tetrafluoroborate appeared. Sodium nitrite (12.0 g, 174 mmol) was added slowly to this suspension. While the addition, the reaction temperature should be kept the range of 5 ~ 9 °C (Note a). The fine crystals gradually decreased as the diazotization proceeded and the reaction mixture turned pale yellow solution. The rate of the addition had to be slower in the latter half of the addition because the exothermic decomposition of the diazonium salt proceeded more. It took about 90 minutes for the addition of sodium nitrite. The reaction mixture turned orange, unclear solution. After the addition of sodium nitrite, the reaction mixture was stirred for additional 30 minutes at 5 ~ 10 °C, then allowed to warm up to 25 °C.

The reaction mixture was added slowly to an aqueous solution of  $\text{NaHCO}_3$  prepared by 30.0 g (357 mmol) of  $\text{NaHCO}_3$  and 200 mL of water (Note b). The brown, gummy precipitates were removed by decantation and filtration through cotton put loosely on a funnel. The filtrate was extracted with  $\text{CH}_2\text{Cl}_2$  (200 mL  $\times$  2) in a 500 mL separatory funnel. The residual suspension containing the brown precipitates was extracted separately with  $\text{CH}_2\text{Cl}_2$  (100 mL  $\times$  2) (Note c). The  $\text{CH}_2\text{Cl}_2$  layers were combined and dried with anhydrous  $\text{Na}_2\text{SO}_4$  until the solution was clear. Then  $\text{Na}_2\text{SO}_4$  was removed by filtration and the solution was replaced in a 500 mL round-bottomed flask. Well-crushed  $\text{CaH}_2$  (5 g) was added carefully and the solution was thoroughly dried overnight (Note d).

The solvent was removed by distillation. In order to remove  $\text{CH}_2\text{Cl}_2$  as much as possible, the residue was replaced to an 100 mL round-bottomed flask and the distillation was continued by heating with an oil bath. The temperature of the oil bath was gradually raised up to 135 °C,  $\text{CH}_2\text{Cl}_2$  was thoroughly removed (Note e). Although the residue was almost pure, the final product was obtained by the vacuum transfer. The apparatus is shown in Figure 1.

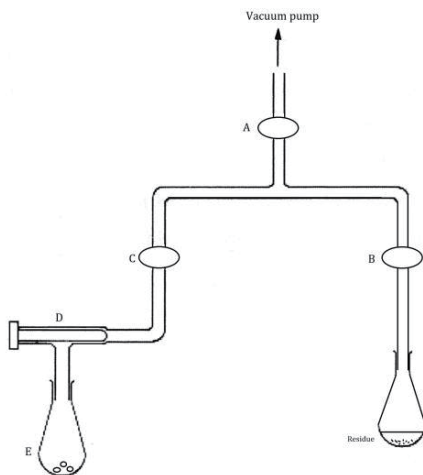


Figure 1. Apparatus for vacuum transfer of **1**.

The flask of the residue was equipped under the cock C. Three NaOH pellets for the storage of the product were put in a 20 mL flask E. The flask E was capped with Young's cock D, which in turn equipped under the cock C. These flasks could be evacuated by the vacuum pump through cock A.

First, the residue was cooled with liquid nitrogen to freeze, and then the flask of the residue was evacuated by opening cock A. Cock C and Young's cock D was opened during the evacuation. After a few minutes cock B was closed and the residue was warmed up to room temperature. This operation was repeated three times. Then the residue was frozen and evacuated again, cock A was closed and the residue was allowed to warm at room temperature. The vacuum transfer was achieved by cooling the flask E with liquid nitrogen (Note f). The obtained pure product was 1.5 g (20%) and could be stored in the flask E capped with Young's cock. The purity of the product was determined according to the NMR spectrum (Figure 2).

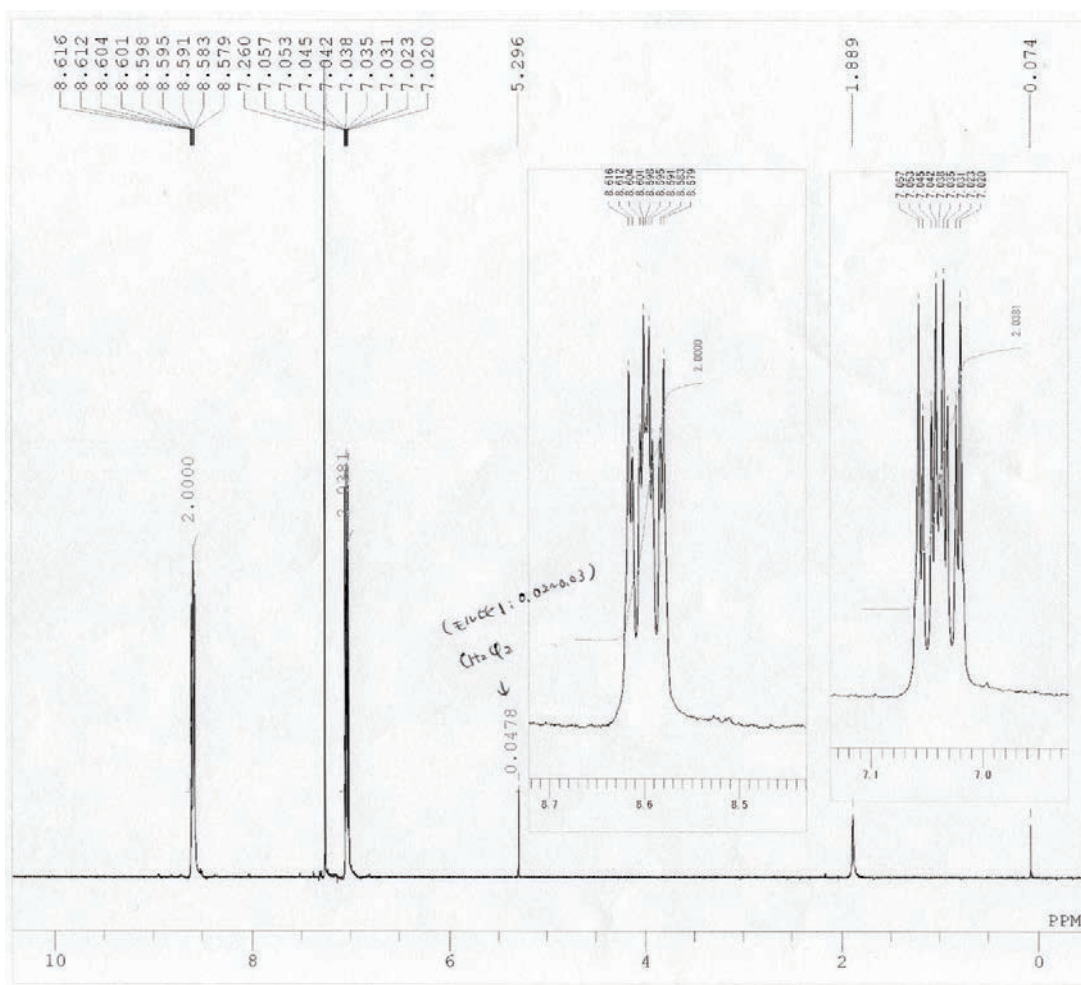


Figure 2.  $^1\text{H}$  NMR spectrum of **1** (400 MHz, in  $\text{CDCl}_3$ ).

**Note a :** The evolution of nitrogen was continuously observed while the addition, the decomposition of the diazonium salt proceeds at the same time at this temperature. If the diazotization is carried out at lower temperature (typically  $-5 \sim 0$  °C), the decomposition of the diazonium salt may be suppressed. But instead, the decomposition will proceed vigorously when the temperature raised to room temperature. Unfortunately, the decomposition accompanied by the heat and the evolution of nitrogen, the reaction may go out of control and the reaction mixture may boil over. (The author experienced the boiling over...)

**Note b :** Although this neutralization was not so exothermic, the reaction mixture should be added carefully for the severe CO<sub>2</sub> gas evolution. On the way of the addition the brown, gummy precipitates would appear. This precipitates would be the polymer compound produced by the polymerization of **1**. This gummy precipitates made the purification difficult. They hardly removed by the filtration with filter paper because of the clogging the filter and increased while the extraction. Therefore, the extraction should be finished as soon as possible.

**Note c :** Because the brown precipitates severely retard the extraction, the extraction separately was faster than the extraction in one time.

**Note d :** The formation of **1** could be confirmed by TLC on silica gel at this stage. The R<sub>f</sub> value was about 0.2 eluted with *n*-hexane : ethyl acetate = 3 :1 (v/v).

**Note e :** The removed CH<sub>2</sub>Cl<sub>2</sub> from 100 mL flask contained the small amount of **1** (about 0.35 g according to <sup>1</sup>H NMR). When the same reaction was applied at an early date, this removed solvent may combine with the organic layer. The boiling point of **1** reported 108 °C / 757 mmHg<sup>[6b]</sup> or 104–105 °C.<sup>[4]</sup> In order to obtain the product in high purity, the complete removal of CH<sub>2</sub>Cl<sub>2</sub> is very important. However, the temperature of the heating bath should be lowered when **1** was almost distilled.

**Note f :** Pure **1** froze by cooling at  $-40$  °C. Containing CH<sub>2</sub>Cl<sub>2</sub> caused the lowering the freezing temperature.

According to Figure 2, **1** exhibits the signals of 8.62 ~ 8.58 ppm (2,6-positions) and 7.06 ~ 7.02 ppm (3,5-positions). The purity of **1** can be estimated to 97% by the comparison with the integration of the signal of CH<sub>2</sub>Cl<sub>2</sub> (5.30 ppm). The splitting pattern of the signals of **1** is considerably complicated, but reasonable and understandable. Figure 3 shows the <sup>1</sup>H NMR spectrum of di-4-pyridylketone in order to show the typical splitting pattern of 4-pyridyl group. Both the signals of 2,6-proton (8.88 ~ 8.85 ppm) and 3,5-proton (7.61 ~ 7.59 ppm) are split into four peaks. Although the splitting system of 4-pyridyl group is magnetically non-equivalent AA'BB' system, the observed signal is resemble to doublet of doublets (dd) pattern in appearance except the intensity of the peaks. The "apparent" coupling constants of di-4-pyridylketone is calculated to 4.3 Hz and 1.6 Hz directly from the spectrum. By the comparison with the typical splitting pattern of 4-pyridyl group, the <sup>1</sup>H NMR signals of **1** is understandable by the splitting of the typical splitting pattern of 4-pyridyl group into two by <sup>19</sup>F nuclear ( $I = 1/2$ ). According to Figure 2, the "apparent" coupling constants of 4-pyridyl protons is calculated to 4.7 Hz and 1.5 Hz, which is compatible to those of di-4-pyridylketone. The coupling constants concerning to <sup>19</sup>F is 8.4 Hz (with 2,6-protons) and 8.8 Hz (with 3,5-protons),<sup>[8]</sup> which were compatible to those reported by Quéguiner *et al.* (8.5 Hz and 9.0 Hz, respectively).<sup>[6d]</sup>

In summary, the author successfully synthesized and isolated 4-fluoropyridine (**1**) in 20% isolation yield. This sample could be stored at least for several weeks without opening. The author recommends this experimental procedure for **1**.

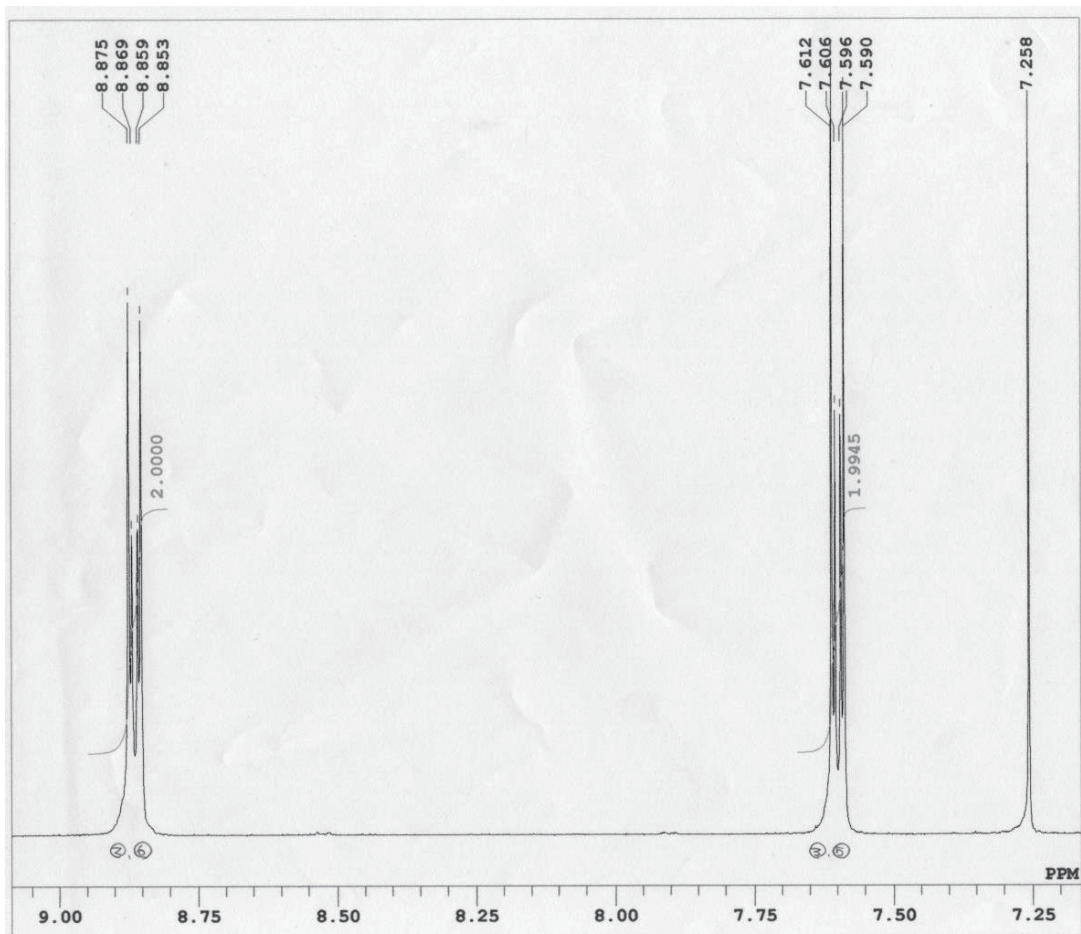


Figure 3. Aromatic region of  $^1\text{H}$  NMR spectrum of di-4-pyridylketone (270 MHz, in  $\text{CDCl}_3$ ).

### Acknowledgement

The author acknowledges the financial support from Institute of Natural Sciences.

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1656.

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- [8] Therefore,  $^1\text{H}$  NMR chemical shifts of **1** containing the “apparent” coupling constants are as follows : 8.60 (ddd,  $J = 8.4, 4.7, 1.5$  Hz, 2H, Py-2,6H), 7.04 (ddd,  $J = 8.8, 4.7, 1.5$  Hz, 2H, Py-3,5H).