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# One-Pot Synthesis of Chloropyridines from Aminopyridines via Diazotization

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**Abstract.** A method for synthesis of chloropyridines from pyridinyl trifluoromethanesulfonates in acetonitrile in the presence of hydrochloric acid was developed. One-pot synthesis of chloropyridines from aminopyridines via diazotization was presented. Pyridyl triflates were obtained in this reaction in situ. This method provides good yields of the target products.

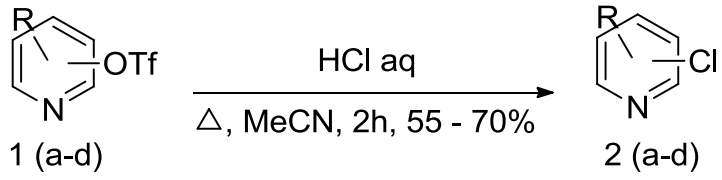
## Introduction

Halogenated pyridines are widely used in organic synthesis in cross-coupling reaction (Stille, Suzuki, Heck and Sonogashira reactions), in nucleophilic substitution of amines, alcohols and thiols, as intermediates for the preparation of drug substances [1-3].

The general method of chlorinated pyridines synthesis is the reaction of hydroxypyridines with traditional chlorinating agents ($SOCl_2$, $POCl_3$ or $PCl_5$). To achieve this other chlorinating agents ($CCl_4$, $Cl_3CCCl_3$, $Cl_3CCOCCl_3$, $Cl_3CCN$, $Cl_3CCONH_2$) combined with triphenylphosphine ($PPh_3$) were recently used [4].

Recently we proposed a convenient method for the synthesis of pyridyl trifluoromethanesulfonates (pyridyl triflates) [5]. Triflate group is a good leaving group, and allows using pyridyl triflates for highly functionalized pyridines obtaining.

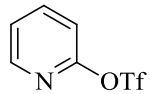
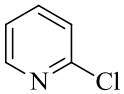
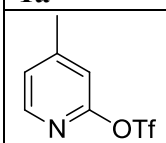
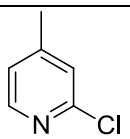
We found out that pyridyl triflates (**1a-d**) are readily converted into the corresponding chloropyridines (**2a-e**) in acetonitrile in the presence of hydrochloric acid. Good yields (Scheme 1-2) and the complete conversion of the starting substrates (**1a-d**) were achieved.

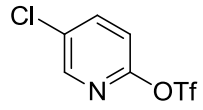
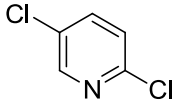
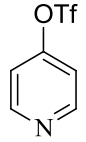
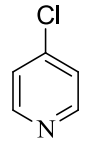



1 (a-d) 2 (a-d)

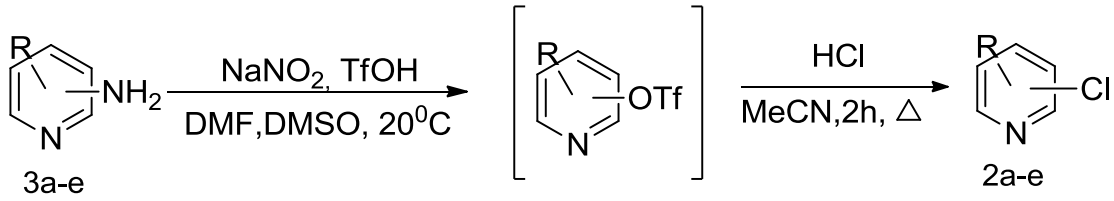
Scheme 1

Table 1: The synthesis of chloropyridines (**2a-d**) from pyridinyl trifluoromethanesulfonates **(1a-d)**

| Substrate | Product | Time, h | Yield, % | m.p.°C (m.p. Lit.°C) |
|---|---|---|---|---|
|  **1a** |  **2a** | 2 | 55 | Oil |
|  **1b** |  **2b** | 2 | 70 | Oil |

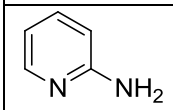
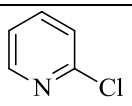
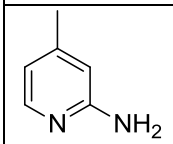
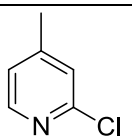
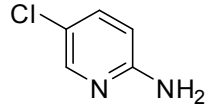
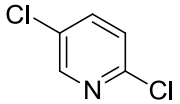
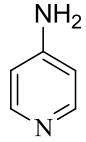
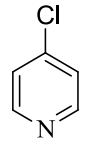
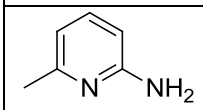
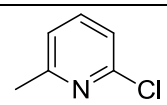
| Substrate | Product | Time, h | Yield, % | m.p.°C (m.p. Lit.°C) |
|---|---|---|---|---|
|  **1c** |  **2c** | 2 | 68 | 58-60°C (60°C [6]) |
|  **1d** |  **2d** | 2 | 60 | Oil |

An attempt to improve the developed method was made. Diazotization of aminopyridines (**3a-e**) was carried out in the presence of trifluoromethanesulfonic acid in dimethylformamide with small additions of dimethyl sulfoxide. Intermediate pyridyl triflates were not isolated; instead acetonitrile and hydrochloric acid were added to the reaction mixture (Scheme 2).




Scheme 2

Table 2: The synthesis of chloropyridines (**2a-e**) from aminopyridines (**3a-e**)

| Substrate | Product | Time, h | Yield, % | mp (°C) (Lit. mp°C) |
|---|---|---|---|---|
|  **3a** |  **2a** | 3 | 60 | Oil |
|  **3b** |  **2b** | 3 | 70 | Oil |
|  **3c** |  **2c** | 3 | 68 | 58-60°C (60°C [6]) |
|  **3d** |  **2d** | 3 | 68 | Oil |
|  **3e** |  **2e** | 3 | 60 | Oil |

Notably the conversion of the starting aminopyridines (**3a-e**) is complete and formation of by-hydroxypyridine is not observed.

In summary, a convenient and economic one-step method for the synthesis of chloropyridines from aminopyridines through diazotization was suggested.

## Experimental part

$^{1}H$, $^{13}C$ NMR spectra were recorded on a Bruker AC 300 (300 MHz) spectrometer with tetramethylsilane (TMS) as the internal standard; there is the solvent on the text. Melting points were determined on melting point system MP50. The identification of obtained compounds was performed by comparing the analytical and physical-chemical characteristics as the authentic sample synthesized by known methods.

GC-MS analysis was performed on Agilent gas chromatograph with a quadrupole mass detector (EI, 70 eV), a carrier gas – helium. Reaction progress was monitored by TLC using Silufol UV-254 with UV detection. Eluent for TLC: hexane: ethyl acetate 3:1.

Trifluoromethanesulfonic acid, aminopyridines (**3 a-e**), DMSO, DMF were acquired from Sigma–Aldrich and used without further purification.

**A general experimental procedure of chloropyridines (2a-d) synthesis from pyridinyl trifluoromethanesulfonates (1a-d) in acetonitrile in the presence of hydrochloric acid is as follows:**

The solution of hydrochloric acid (38%, 4 ml) was added to the mixture of pyridyl triflate (2 mmol) in 1 mL of MeCN. The mixture was heated to 80 °C, kept at this temperature for 2 h. The mixture was then cooled, poured into water (40 mL), treated with 10% aqueous $Na_2CO_3$ (4 mL) until pH =10, and then extracted with $CH_2Cl_2$ (3 x 15 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, and the solvent evaporated in vacuum. The products 2a-d were purified by silica gel flash chromatography, eluent $CH_2Cl_2$.

2-chloropyridine (2a): oil, 55%, the NMR $^{1}H$, $^{13}C$ data is in good agreement with [7];
m/z: 113 (M+, 70), 78 (100), 60 (5), 51 (25), 38 (7), 26 (10).

2-chloro-4-methylpyridine (2b): oil, 70%, the NMR $^{1}H$, $^{13}C$ data is in good agreement with [8];
m/z: 127 (M+, 100), 91 (90), 65 (38), 51 (10), 43 (20), 39 (17).

2,5-dichloropyridine (2c): 68%, mp 58-60°C (mp Lit.60°C [6]);
m/z: 147 (M+, 100), 112 (75), 87 (10), 76 (50), 62 (15), 50 (42), 36 (5).

4-chloropyridine (2d): oil, 60%, the NMR $^{1}H$, $^{13}C$ data is in good agreement with [9];
m/z: 113 (M+, 100), 86 (7), 78 (60), 60 (5), 51 (23), 43 (7), 36 (5).

**A general experimental procedure of chloropyridines (2a-e) synthesis via diazotization of aminopyridines (3a-e) is as follows:**

A mixture of aminopyridine (2 mmol) and $NaNO_2$ (5 mmol, 0.35 g) was ground with a pestle in an agate mortar until a homogeneous mixture formed. The mixture was slowly over 10 minutes added to solution of dimethylformamide (4 mL), trifluoromethanesulfonic acid (6 mmol, 0.54 mL) and dimethylsulfoxide (1.3 mmol, 0.1 mL), cooled to 5-7 °C. The resulting mixture was kept at 5-7 °C for 5 minutes and left for 30 minutes at room temperature. Then the reaction mixture was added of acetonitrile (1 mL), hydrochloric acid (38%, 4 ml) and heated to 80 ° C for 2 hours to complete the reaction. Isolation of chloropyridines (2a-e) is carried out by the method described above.

2-chloro-6-methylpyridine (2e) oil, 55%, the NMR $^{1}H$, $^{13}C$ data is in good agreement with [10];
m/z: 127 (M+, 100), 92 (65), 65 (30), 39 (10).

## Acknowledgments

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