SOME NEW 2-SUBSTITUTED 5-TRIFLUOROMETHYLPYRIDINES

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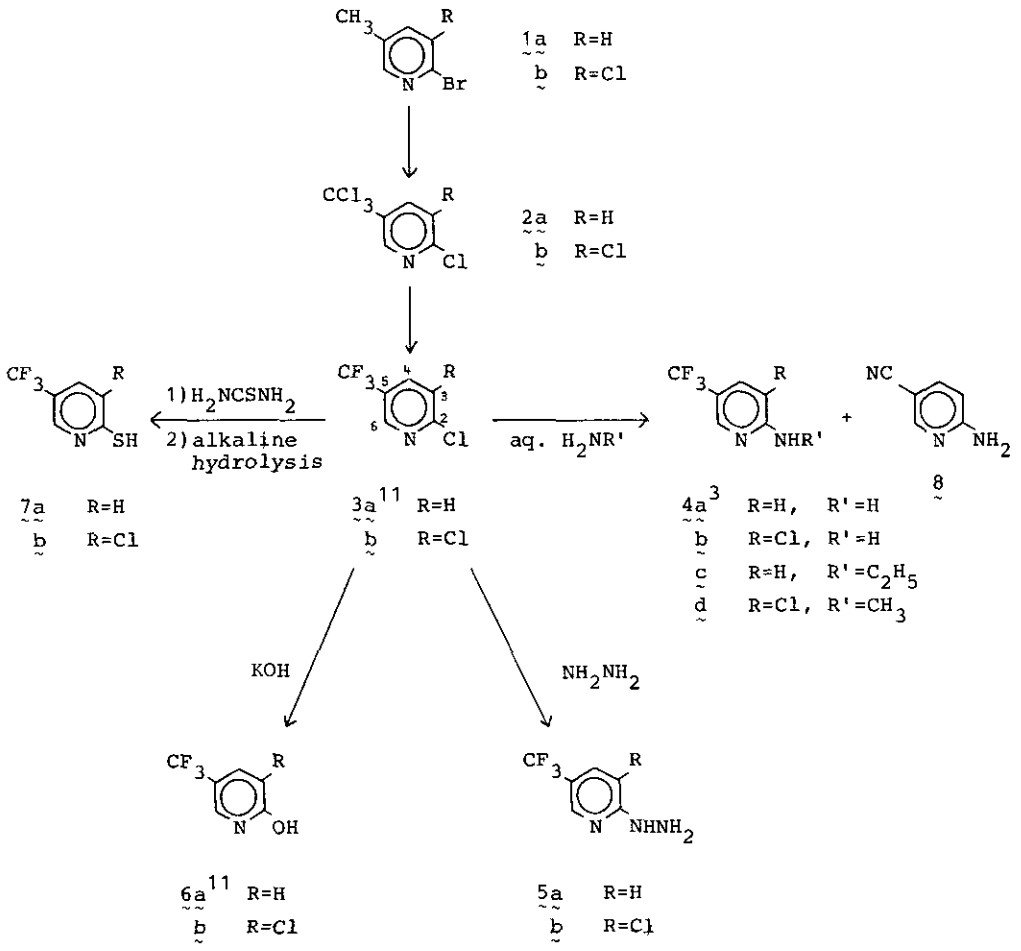
Abstract —— The preparation of the derivatives of 2-amino-, hydrazino-, hydroxy-, and mercapto-5-trifluoromethylpyridines via 2-chloro precursors is described. Experimental and spectral data of the products together with those of the precursors are presented.

During the past twenty years, the chemistry of fluorine-containing compounds has been tremendously developed. Owing to their unique properties, such as high thermal stability and lipophilicity, fluoro organic compounds have been frequently applied to bio-related materials, medicines and agrochemicals.[1] More than ten pesticides containing trifluoromethyl aromatics, especially benzotrifluoride (hereafter BTF) analogs have been manufactured and used worldwidely.
Although the research on bio-active benzotrifluorides[2] has been extensively developed utilizing the readily available chloro BTFs as starting material, few studies were done on the corresponding pyridines.[3] In the course of the research to discover unique pesticides having trifluoromethylpyridine moiety, three unique pesticides,[4-6] whose superior properties might be considered to be arisen from 3-trifluoromethylpyridine moiety, were discovered. In pesticides chemistry, the significance of 3-trifluoromethylpyridine as well as that of BTF has been well recognized. Here, we wish to report the result of a series of our research on 3-trifluoromethylpyridines from the view of synthetic chemistry. Several 2-substituted 5-trifluoromethylpyridines, such as amino 4, hydrazino 5, hydroxy 6, and mercapto 7 derivatives[10] were synthesized from the same starting materials 3 in good yield. And their structures were fully characterized by spectrometric analyses (including mass spectroscopy) and satisfactory microanalyses. Scheme 1 and Tables 1 and 2 present summary of the data. All of the compounds 3-7 except 3a[11], 4a[3] and 6a[11] are new.



Scheme 1 Preparation of 2-Substituted 5-Trifluoromethylpyridines via 2-Chloro Precursors.

Although many practical processes to produce substituted anilines through ammonolysis are known, preparation of p-amino BTF[12] from commercially available p-chloro BTF and aqueous ammonia is not considered as a practical method, probably due to low reactivity of the chlorine and hydrolytical unstability of p-amino BTF. A combination of cuprous chloride and potassium fluoride in ethanol at 200°C gave some improved results.[13]

On the other hand, like other activated 2-chloropyridines, ammonolysis of 2-chloro-5-trifluoromethylpyridine 3a with 28% of aqueous ammonia proceeded at around 135°C

Table 1. Experimental and Spectral Data of 2-Substituted 5-Trifluoromethylpyridines.

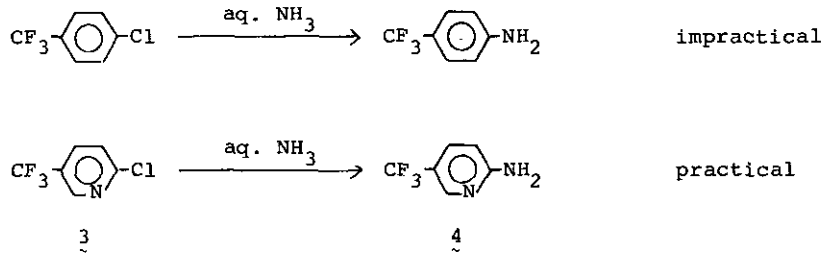
Compound[a] No.	Yield %	mp(°C) bp(°C/mmHg)	IR[b], ν(cm^{-1})	^{1}H Chemical Shifts[c], δ(ppm)					M.S.
				Solvent[d]	H-3	H-4	H-6	Other H[e]	M$^+$
3a	54.5	30.2 (139-141)	1109 1140 1330 1591 1683	C	7.49d	7.92dd	8.66d*	-	181
3b	80.4	(118-130/96)	1153 1169 1317 1360 1589	C	-	8.03dd	8.58d*	-	215
4a	75.0	49.5-51.5	818 1070 1095 1315 1605	C	6.49d	7.58dd	8.30d*	†	162
4b	82.9	90-92	1098 1135 1324 1350 1630	C	-	7.69dd	8.21d*	†	196
4c	78.9	75-77	820 1108 1322 1618	C	6.30d	7.53dd	8.27d*	†,**	190
4d	83.8	38-40.5	1111 1329 1640	C	-	7.56dd	8.22d*	†,***	210
5a	89.7	62-66	818 1070 1100 1322 1615	C	6.99d	7.67dd	8.35d*	†	177
5b	85.8	58-60	1080 1115 1160 1310 1610	C	-	7.63dd	8.33d*	†	211
6a	87.2	154-156	1095 1165 1320 1620 1655	A	6.59*	7.68*	8.01*	††	163
6b	75.2	165-166	1120 1295 1605 1690	A	-	7.91*	8.00*	††	197
7a	53.3	147-150	1120 1310 1570 1635	A	7.87*	8.15*	8.85*	††	179
7b	40.4	125-128	1130 1160 1285 1580 1635	A	-	7.97*	8.14*	††	213

[a] Satisfactory microanalyses were obtained. [b] Only most intensive absorption bands are reported. [c] Spin-coupling patterns of either H-6 in all cases or H-3 and H-4 in 6a-7b(*) are not clear. H-6 of 3a is checked to be doublet on a JEOL FX-270 spectrometer. Symbols d or dd are reported in case of 3a-3b. [d] A: hexadeuteroacetone C: deuterochloroform. [e] † N-H between 3.8 and 6.8, broad. †† (thio)pyridone's protons around 9, flat. ** CH_3 at 1.27t and CH_2 at 3.36dq. *** CH_3 at 3.10d.

Table 2. ^{13}C Chemical Shifts of 2-Substituted 5-Trifluoromethylpyridines. (ppm)

Compound No.	Solvent[a]	C-2	C-3	C-4	C-5	C-6	CF_3	Other C
3a	C	155.57	124.77	135.92q	126.10q	147.12q	123.55q	-
3b	C	153.33	131.52	135.97q	126.98q	144.38q	122.72q	-
4a	C	161.25	108.15	134.75q	116.27q	145.75q	124.63q	-
4b	C	157.10	114.41	133.65q	117.40q	143.79q	123.46q	-
4c	C	160.76	105.61	134.35q	115.99q	146.24q	124.24q	*
4d	C	156.36	115.00	132.60q	115.54q	143.89q	124.07q	**
5a	C	162.91	106.00	134.55q	117.98q	145.65q	124.58q	-
5b	C	157.04	114.31	133.08q	117.15q	143.35q	124.53q	-
6a	C	165.06	121.06	134.16q	111.18q	137.58q	121.55q	-
6b	C	161.15	126.93	135.53q	111.43q	132.65q	122.43q	-
7a	A	161.44	126.34	135.19q	125.25q	147.41q	121.55q	-
7b	D	177.97	125.56	135.62q	113.43q	131.22q	122.62q	-

[a] A: hexadeuteroacetone C: deuterochloroform D: hexadeuterodimethyl sulfoxide
* CH_2 at 36.77 and CH_3 at 14.47 ** CH_3 at 28.55



3 4

Scheme 2

without any catalyst to give almost pure 4a in good yield (see Scheme 2). At 180°C, nitrile 8 was formed as a by-product, which was identified with the authentic sample.[14] Ammonolysis of 3b proceeded even at 100°C. Chlorination of 4a in concentrated hydrochloric acid at 50-60°C by chlorine gas alternatively gave 4b. The reaction of 4 with hydrazine took place even at near room temperature (at 40°C) to give 5 in good yield. Hydrolysis of 3 with potassium hydroxide as a base in refluxing tert-butanol gave the 2-pyridones 6. Compound 6a was already synthesized in tedious manner by treating 3a with silver acetate in acetic acid under nitrogen at 140°C for 45 h.[11] 2-Thiopyridones 7 were prepared by treating the corresponding 3 with equimolar thiourea followed by alkaline hydrolysis without isolation of the resulting intermediate, isothiuronium salt.

As shown in Scheme 1, 5-trifluoromethylpyridines 3 as starting materials were prepared by side chain chlorination of corresponding 5-methylpyridines followed by fluorination by antimony trifluoride.[15,16] At the early stage of the chlorination, dark red vapor, eliminated bromine from the pyridines 1, was observed. It should be noted in the fluorination process from 2 to 3 that the scrupulous reaction time and temperature brought a fruitful result. In some cases, longer reaction time caused the decomposition of the product, while lower temperature resulted in incomplete fluorination affording 5-chlorodifluoromethylpyridines. Compounds 3 were thus synthesized and purified by distillation as described in experimental section. Through these preparations, it is proved that reaction of chloro derivatives 3 with several nucleophiles proceeds smoothly, like other activated 2-halopyridines. It is also notable that 4 and 6 are stable even in alkaline condition. Although, corresponding p-hydroxy BTF, for example, is reported to be extremely labile in the presence of base.[16] Thus, a variety of these functionalized compounds 4-7 have been obtained and used as versatile intermediates for agrochemical syntheses,

even though the corresponding benzenoid compounds remain hard to prepare.[17] Furthermore, a direct preparation of 3 from 3-methylpyridine by simultaneous chlorination and fluorination will be reported elsewhere.

EXPERIMENTAL SECTION

General procedures

Melting points were obtained on a Yanaco Melting Point Apparatus (Model MP J-3) and are uncorrected. Microanalyses were performed using a Yanaco CHN Corder (Model MT-3). Infrared spectra were recorded as potassium bromide pellets on a Shimadzu Spectrometer (Model IR-400). Proton NMR spectra were obtained on a JEOL FX-60 spectrometer. Proton noise-decoupled carbon-13 natural abundance NMR spectra were taken on the same instrument. The chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were obtained with a JEOL JMS D-300 mass spectrometer at Toray Research Center in Ohtsu, Shiga, Japan.

Preparation of starting materials

2-Chloro-5-trifluoromethylpyridine 3a Diazotization of 2-amino-5-methylpyridine afforded 2-bromo-5-methylpyridine 1a according to the procedure of Craig.[18] To the refluxing solution of 1a (172 g, 1.0 mol) and benzoyl peroxide (48 g, 0.2 mol) in dry carbon tetrachloride (1300 ml) was introduced dry chlorine gas for 8 h with inner irradiation by a high pressure mercury lamp immersed in the reaction flask. The mixture was then cooled, aerated for 30 min, and washed with water until the washings showed almost neutral. Evaporation of carbon tetrachloride from the solution after drying over anhydrous sodium sulfate gave a pale yellow liquid, which solidified on standing. The product, 2-chloro-5-trichloromethylpyridine 2a was obtained by filtration followed by washing with dry n-hexane, in 65.8% yield (152 g), mp 52-54°C. A well mixed mixture of 2a (23.1 g, 0.1 mol) and pulverized dry antimony trifluoride (24.0 g) was placed with well stirring in a 500 ml flask which was quickly heated up using a pre-heated oil bath (210°C). The mixture began to melt and gas evolution and vigorous reflux soon occurred. Ten minutes sharp after the temperature of the mixture reached at 170°C, the oil bath was quickly removed. After being cooled, the reaction mixture was washed with a mixture of ice and concentrated hydrochloric acid, followed by extraction with methylene chloride three times. Combined extracts were washed with water, dried

over anhydrous sodium sulfate and rotary-evaporated. Distillation of the residue under atmospheric pressure gave 9.9 g (54.5%) of 3a, bp 139-141°C, mp 30.2°C, mass spectrum m/e 181 (M^+).

2,3-Dichloro-5-trifluoromethylpyridine 3b Diazotization of 2-amino-3-chloro-5-methylpyridine followed by side chain chlorination gave 2,3-dichloro-5-trichloromethylpyridine 2b in 66.0% yield, bp 158°C/23 mmHg. Fluorination of 2b in the same manner as described above except using 20 min sharp reaction time instead of 10 min in case of 2a gave 3b in 80.4% yield based on consumed 2b, bp 118-120°C/96 mmHg, mass spectrum m/e 215 (M^+).

Preparation of 2-substituted 5-trifluoromethylpyridines

2-Amino-3-chloro-5-trifluoromethylpyridine 4b Compound 3b (6.5 g, 30 mmol) and 28% of aqueous ammonia (20 ml) were placed in a 50 ml autoclave, then subjected to heat for 24 h at 100°C, and additional 5 h at 125°C (inner pressure was around 2 atm). After sufficient cooling, the crystal 4b formed was collected (1.5 g), which showed mp 90-92°C. Extraction of the aqueous layer with methylene chloride gave additional 3.4 g of 4b. Total 4.9 g of 4b was obtained in 82.9% yield.

2-Amino-5-trifluoromethylpyridine 4a and 6-amino-nicotinonitrile 8 Compound 3a (5.4 g, 30 mmol) and 28% of aqueous ammonia (20 ml) were charged in the same autoclave, and heated for 24 h at 135°C. After being cooled, the content was extracted with methylene chloride, and the organic layer was dried over anhydrous sodium sulfate. Evaporation of methylene chloride gave 3.65 g of 4a in 75.0% yield, mp 49.5-51.5°C (melting point was not reported in literature.[3]) When the same mixture was reacted at 180°C for 8 h (inner pressure was 25-28 atm), a tarry product was obtained. After usual work-up, separation of the product by silica gel column chromatography followed by recrystallization from n-hexane gave 1.9 g of 4a in 39% yield and 0.8 g of 8 in 22% yield, mp 158-160°C (lit.[14] 164°C), mass spectrum m/e 119 (M^+).

2-Ethylamino-5-trifluoromethylpyridine 4c Reaction of 3a (18.1 g, 0.1 mol) with 70% of aqueous ethylamine (50 g) in ethanol(100 ml) at 60°C for 5.5 h gave 15.0 g of crystal 4c in 78.9% yield, mp 75-77°C, mass spectrum m/e 190 (M^+).

3-Chloro-2-methylamino-5-trifluoromethylpyridine 4d Reaction of 3b (10.8 g, 50 mmol) with methylamine hydrochloride (6.8 g) and anhydrous potassium carbonate (6.9 g) in ethanol (50ml) at 60°C for 7 h then at 90°C for 1.5 h gave 8.8 g of 4d, in 83.8% yield, mp 38-40.5°C, mass spectrum m/e 210 (M^+).

3-Chloro-2-hydrazino-5-trifluoromethylpyridine 5b A solution of 3b (5 g, 23 mmol) and 100% of hydrazine hydrate (12.5 g) in ethanol (40 ml) was heated at 40°C for 24 h. After usual work-up, 4.2 g of 5b was obtained in 85.8% yield, mp 58-60°C, mass spectrum m/e 211 (M^+).

2-Hydrazino-5-trifluoromethylpyridine 5a In the same fashion as described above, 5a was obtained in 89.7% yield, mp 62-66°C. However, it is notable that only this compound among those described here is unstable, even if stored under nitrogen atmosphere. Soon after the preparation, the crystal gives satisfactory ^{13}C NMR spectrum. However, it gradually changed into a tarry crystal. On mass spectrum, besides m/e 177 (M^+), a few weak peaks in the region of higher molecular weight than 177 were observed.

3-Chloro-5-trifluoromethyl-2-pyridone 6b Compound 3b (4.5 g, 20.8 mmol) was added to a solution of 2.7 g of potassium hydroxide dissolved in tert-butanol (100 ml), and the mixture was reacted at the reflux temperature for 1 h with well stirring. After being cooled, the reaction mixture was acidified with concentrated hydrochloric acid. Evaporation under reduced pressure followed by washing with water gave a solid. Recrystallization from ethanol gave 3.1 g of 6b in 75.2% yield, mp 165-166°C, mass spectrum m/e 197 (M^+).

5-Trifluoromethyl-2-pyridone 6a In the substantially same manner as described above, 6a was prepared in 87.2% yield, mp 154-156°C (lit.[11] 145-147.8°C), mass spectrum m/e 163 (M^+).

5-Trifluoromethyl-2-thiopyridone 7a A mixture of 3a (4.0 g, 22.1 mmol) and thiourea (1.67 g) in ethanol (30 ml) was heated for 3 h under reflux. Thereafter, a solution of 1.86 g of potassium hydroxide in water (5 ml) was added dropwise to the mixture, which was heated for additional 1 h. After being cooled, the reaction mixture was poured into diluted aqueous alkaline solution and washed with methylene chloride. The aqueous solution was acidified with acetic acid, then the product was extracted with methylene chloride. The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of methylene chloride gave 2.1 g of 7a in 53.3% yield, mp 147-150°C, mass spectrum m/e 179 (M^+).

3-Chloro-5-trifluoromethyl-2-thiopyridone 7b In the substantially same manner as described above, 1.9 g of 7b was obtained from 4.75 g of 3b in 40.4% yield, mp 125-128°C, mass spectrum m/e 213 (M^+).

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