A CONVENIENT ONE-POT SYNTHESIS OF 6-TRIFLUOROMETHYL-PYRIDINES

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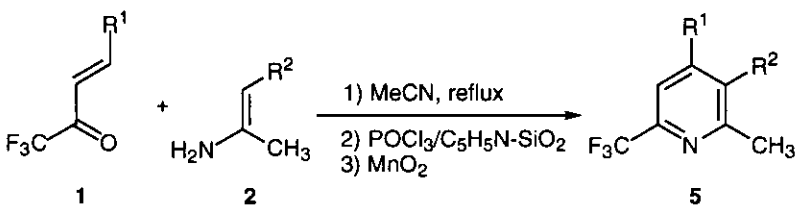
Abstract: - α,β-Unsaturated trifluoromethyl ketones (**1**) react with primary enamines (**2**) such as β-aminocrotononitrile and β-aminocrotonates in the presence of phosphorus oxychloride / pyridine adsorbed on silica gel and manganese dioxide, providing good to high yields of 6-trifluoromethylpyridines (**5**).

Pyridine derivatives have been found to possess biological activity as antitumor antibiotics,[1] herbicides,[2] and insecticides.[3] In particular, trifluoromethyl-substituted pyridines have recently attracted attention because of their potential ability as agrochemicals[4] and medicines.[5] Therefore, we have recently synthesized various 4-trifluoromethylpyridines.[6]

The positional variation of the trifluoromethyl group in an organic molecule often causes a considerable difference in its biological activity.[7] With the aim of discovering higher biologically active pyridines, we have tried to prepare the 6-trifluoromethylpyridines.

This paper describes a convenient one-pot synthesis of the 2-methyl-6-trifluoromethylpyridines (**5**) from α,β-unsaturated trifluoromethyl ketones (**1**) and enamines (**2**) (Scheme 1).



1 **2** **5**

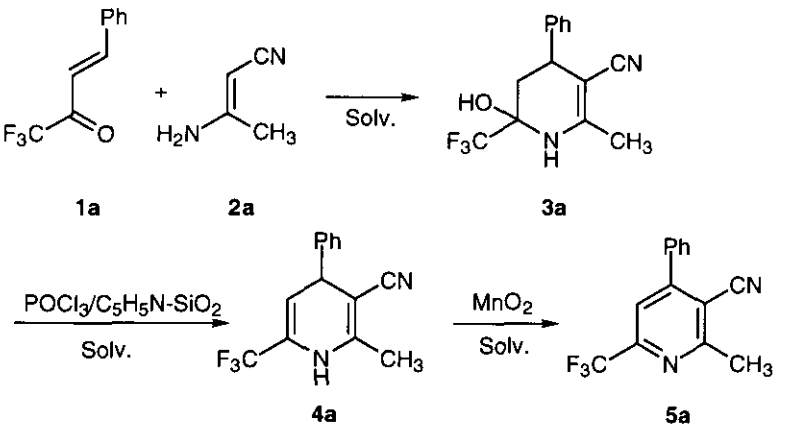
Scheme 1

Although several methods have already been reported for the synthesis of the 6-trifluoromethylpyridines, they sometimes require long reaction times or intractable starting materials[8], or the success of these methods depends upon the reactivity of the substrate.[9] Furthermore, most of the synthetic methods of pyridines are not applicable to trifluoromethyl-substituted compounds. In practice, the procedure described in our previous paper[10] failed to give the desired **5** because of the high stability of the intermediate hydroxypyridines (**3**).

Therefore, we have decided to establish a method for the one-pot synthesis of **5** *via* the dehydration of **3** and then the oxidation of **4**. Previously, we developed an effective dehydration agent, phosphorus oxychloride / pyridine adsorbed on silica gel ($POCl_3/C_5H_5N$-SiO_2).[11] In the oxidation process, agents of choice include $NaNO_3$/AcOH,[12] HNO_3[13] or activated MnO_2.[14] Of the oxidizing agents studied, the use of MnO_2 led to the highest yields of **5a** (98 % yield based on **4a**). Table 1 shows the one-pot synthesis of

the 6-trifluoromethylpyridines (**5a**) *via* the dehydration of **3a** using $POCl_3/C_5H_5N$-SiO_2 followed by the oxidation of **4a** using MnO_2. The use of acetonitrile as a solvent provided the optimum result; refluxing in acetonitrile induced both a short reaction time and the highest yield of **5a**.

Table 1. Screening of the solvents for the one-pot synthesis of **5a**



1a **2a** **3a** **4a** **5a**

Entry	Solvent	Time/h			Yield[d]/%
		1[a]	2[b]	3[c]	of **5a**
1	CH_2ClCH_2Cl	10	2	1	83
2	$CH_3CO_2C_2H_5$	7	2	2	73
3	C_2H_5OH	2	7	4	69
4	benzene	5	3	2	78
5	THF	7	2	4	47
6	CH_3CN	3	3	3	91

a) Reaction time required to consume **1a**. b) Reaction time required to consume **3a**. c) Reaction time required to consume **4a**. d) Isolated yield referred to **1a**.

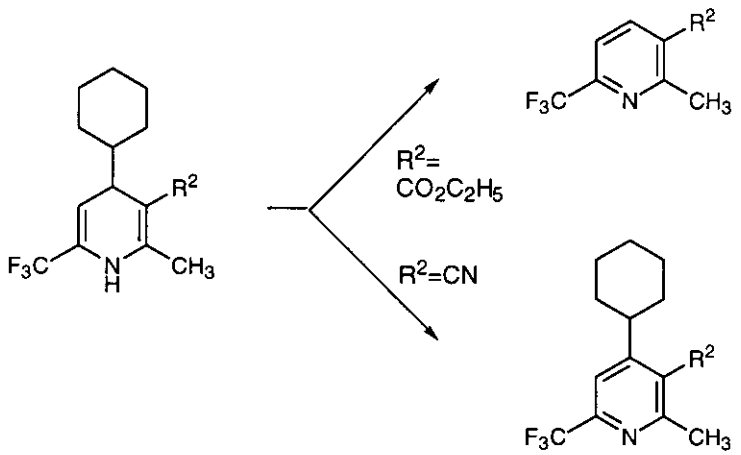
As Table 2 summarizes, the reaction of **1b-h** with **2a** under the same conditions gave the 3-cyano-6-trifluoromethylpyridines (**5b-h**) in good to high yields. The treatment of **1a-h** with ethyl β-aminocrotonate (**2b**) also provided the ethyl 6-trifluoromethylpyridine-3-carboxylates (**5i-p**) in good to high yields.

On the other hand, the expulsion of the R^1 group was observed when this substituent is a cyclohexyl group; this phenomenon has been observed when the substituent in the 4-position is a benzylic group or a secondary alkyl group.[15] Only when the R^2 group was a cyano group, no loss of the cyclohexyl group occurred, thus producing the corresponding cyclohexyl-substituted 3-cyano-6-trifluoromethylpyridine (Scheme 2); this finding has been observed as the substituents in the 3 and 5-positions are sterically smaller.[15] These results indicate that the course of the oxidation reaction is governed both by the stability of the potential leaving carbonium ion and by steric factors such as the size of the groups in the 3-positions.

Table 2. Synthesis of 2-methyl-6-trifluoromethylpyridines (**5**)

Ketone	R^1	R^2	Product	Yield[a] / %
1a	Ph	CN	**5a**	91
1b	4-$CH_3OC_6H_4$	CN	**5b**	79
1c	4-ClC_6H_4	CN	**5c**	92
1d	4-FC_6H_4	CN	**5d**	79
1e	4-$NO_2C_6H_4$	CN	**5e**	77
1f	4-$CF_3C_6H_4$	CN	**5f**	84
1g	2-Furyl	CN	**5g**	87
1h	2-Thienyl	CN	**5h**	87
1a	Ph	$CO_2C_2H_5$	**5i**	94
1b	4-$CH_3OC_6H_4$	$CO_2C_2H_5$	**5j**	78
1c	4-ClC_6H_4	$CO_2C_2H_5$	**5k**	90
1d	4-FC_6H_4	$CO_2C_2H_5$	**5l**	94
1e	4-$NO_2C_6H_4$	$CO_2C_2H_5$	**5m**	96
1f	4-$CF_3C_6H_4$	$CO_2C_2H_5$	**5n**	91
1g	2-Furyl	$CO_2C_2H_5$	**5o**	85
1h	2-Thienyl	$CO_2C_2H_5$	**5p**	86

a) Isolated yields referred to **1**.



Scheme 2

The structure of the 6-trifluoromethylpyridines (**5**) has been elucidated by comparing their ^{13}C and ^{19}F NMR spectra with those of the corresponding 4-trifluoromethylpyridines (**6**).[6]

In summary, we have found a convenient method for the one-pot synthesis of the 6-trifluoromethylpyridines (**5**) *via* the reaction of α,β-unsaturated trifluoromethyl ketones (**1**) with enamines (**2**) in the presence of $POCl_3/C_5H_5N$-SiO_2 and MnO_2. These 6-trifluoromethylpyridines show

higher herbicidal activity than the 4-trifluoromethyl derivatives. Moreover, some of these pyridines have been found to possess potent antifungal activity.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP-S2 micro melting point apparatus and are uncorrected. IR spectra were measured with a Perkin Elmer FT-IR 1640 spectrometer. ^{1}H NMR spectra were recorded with a JEOL α-400 spectrometer using TMS as the internal standard. ^{19}F NMR spectra were obtained on the same apparatus using TFA as the external standard. MS spectra (EI, 70 eV) were obtained on a Shimadzu QP-1000 spectrometer. Elemental analyses were performed on a Yanaco CHN Corder MT-3 elemental analyzer.

All the commercially available reagents were used without further purification. Starting materials (**1a-h**) were prepared according to the following literature procedure.[16]

General Procedure for the Synthesis of α,β-Unsaturated Trifluoromethyl Ketones (1a-h): To a stirred solution of aldehydes (10 mmol), acetic acid (0.9 g, 15 mmol), and piperidine (0.9 g, 10 mmol) in benzene (10 mL) at rt was added dropwise a solution of trifluoroacetone (4.5 g, 40 mmol) in benzene (10 mL). The mixture was stirred for 24 h at this temperature and then quenched with a saturated aqueous solution of ammonium chloride. The organic layer was washed with water, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with benzene/hexane (1/1).

General Procedure for the Synthesis of 2-Methyl-6-trifluoromethylpyridines (5): A solution of α,β-unsaturated trifluoromethyl ketones (**1**) (1 mmol) and primary enamines (**2**) (1 mmol) in acetonitrile (4 mL) was refluxed for 2-3 h. $POCl_3/C_5H_5N$-SiO_2 (0.9 g) was then added and the mixture was further refluxed while being stirred for 3-4 h. MnO_2 (1.4 g, 16 mmol) was then added and the mixture was further refluxed while being stirred for 2-3 h. After evaporation of the solvent, the residue was chromatographed on silica gel using benzene or hexane/CH_3CO_2Et/ (5/1) as the eluent.

3-Cyano-2-methyl-4-phenyl-6-trifluoromethylpyridine (5a): mp 166-168 °C (EtOH); IR (Nujol)ν = 2223 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.94 (s, 3H), 7.56-7.59 (m, 3H), 7.61-7.63 (m, 2H), 7.66 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.16 (s, 3F); MS *m/z* (rel intensity) 262 (M^+, 100), 193 (21). Anal. Calcd for $C_{14}H_9N_2F_3$: C, 64.12; H, 3.46; N, 10.68. Found: C, 64.17; H, 3.49; N, 10.56.

3-Cyano-2-methyl-4-(4-methoxyphenyl)-6-trifluoromethylpyridine (5b): mp 169-170 °C (EtOH); IR (Nujol)ν = 2226 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.92 (s, 3H), 3.90 (s, 3H), 7.07 and 7.61 (ABq, J = 8.1 Hz, 4H), 7.62 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.14 (s, 3F); MS *m/z* (rel intensity) 292 (M^+, 100), 180 (26). Anal. Calcd for $C_{15}H_{11}N_2OF_3$: C, 61.65; H, 3.79; N, 9.59. Found: C, 61.64; H, 3.80; N, 9.59.

3-Cyano-4-(4-chlorophenyl)-2-methyl-6-trifluoromethylpyridine (5c): mp 122-123 °C (EtOH); IR (Nujol)ν = 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.94 (s, 3H), 7.56 (s, 4H), 7.63 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.18 (s, 3F); MS *m/z* (rel intensity) 296 (M^+, 100), 241 (20). Anal. Calcd for $C_{14}H_8N_2ClF_3$: C, 56.68; H, 2.72; N, 9.44. Found: C, 56.67; H, 2.74; N, 9.37.

3-Cyano-4-(4-fluorophenyl)-2-methyl-6-trifluoromethylpyridine (5d): mp 149-150 °C (EtOH); IR (Nujol)ν = 2221 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.94 (s, 3H), 7.25-7.29 (m, 2H), 7.61-7.65 (m, 3H); ^{19}F NMR ($CDCl_3$) δ = -31.3- -31.1 (m, 1F), 9.18 (s, 3F); MS *m/z* (rel intensity) 280 (M^+, 100). Anal. Calcd for $C_{14}H_8N_2F_4$: C, 60.01; H, 2.88; N, 10.00. Found: C, 59.98; H, 2.87; N, 9.83.

3-Cyano-2-methyl-4-(4-nitrophenyl)-6-trifluoromethylpyridine (5e): mp 155-156 °C (EtOH); IR (Nujol)ν = 2234 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.97 (s, 3H), 7.67 (s, 3H), 7.44 and 7.80 (ABq, J = 8.8 Hz,

4H); ^{19}F NMR ($CDCl_3$) δ = 9.21 (s, 3F); MS *m/z* (rel intensity) 307 (M^+, 100), 261 (31), 249 (29), 241 (27), 234 (22), 192 (33). Anal. Calcd for $C_{14}H_8N_3O_2F_3$: C, 54.73; H, 2.62; N, 13.68. Found: C, 54.58; H, 2.60; N, 13.56.

3-Cyano-2-methyl-6-trifluoromethyl-4-(4-trifluoromethylphenyl)pyridine (5f): mp 86-87 °C (EtOH), IR (Nujol) ν = 2229 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.96 (s, 3H), 7.66 (s, 1H), 7.74 and 7.85 (ABq, J = 8.3 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ = 9.23 (s, 3F), 14.98 (s, 3F); MS *m/z* (rel intensity) 330 (M^+, 100). Anal. Calcd for $C_{15}H_8N_2F_6$: C, 54.56; H, 2.44; N, 8.48. Found: C, 54.02; H, 2.41; N, 8.47.

3-Cyano-4-(2-furyl)-2-methyl-6-trifluoromethylpyridine (5g): mp 116-117 °C (EtOH); IR (Nujol) ν = 2229 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.89 (s, 3H), 6.68 (dd, J = 3.7, 2.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 3.7 Hz, 1H), 8.00 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 8.82 (s, 3F); MS *m/z* (rel intensity) 252 (M^+, 100), 223 (27). Anal. Calcd for $C_{12}H_7N_2OF_3$: C, 57.15; H, 2.80; N, 11.11. Found: C, 57.20; H, 2.78; N, 11.13.

3-Cyano-2-methyl-4-(2-thienyl)-6-(trifluoromethyl)pyridine (5h): mp 129-130 °C (EtOH); IR (Nujol) ν = 2221 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.91 (s, 3H), 7.26 (dd, J = 5.1, 3.9 Hz, 1H), 7.65 (dd, J = 5.1, 1.0 Hz, 1H), 7.72 (s, 1H), 7.98 (dd, J = 3.9, 1.0 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.00 (s, 3F); MS *m/z* (rel intensity) 268 (M^+, 100). Anal. Calcd for $C_{12}H_7N_2F_3S$: C, 53.73; H, 2.63; N, 10.44. Found: C, 54.04; H, 2.73; N, 10.22.

Ethyl 2-Methyl-4-phenyl-6-trifluoromethylpyridine-3-carboxylate (5i): oil; IR (Neat) ν = 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.03 (t, J = 7.1 Hz, 3H), 2.70 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 7.36-7.47 (m, 5H), 7.55 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.53 (s, 3F); MS *m/z* (rel intensity) 309 (M^+, 41), 264 (100).. Anal. Calcd for $C_{16}H_{14}NO_2F_3$: C, 62.14; H, 4.56; N, 4.53. Found: C, 62.27; H, 4.72; N, 4.25.

Ethyl 4-(4-Methoxyphenyl)-2-methyl-6-trifluoromethylpyridine-3-carboxylate (5j): mp 34-35 °C (hexane); IR (Nujol) ν = 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.11 (t, J = 7.1 Hz, 3H), 2.67 (s, 3H), 3.85 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 6.97 and 7.35 (ABq, J = 8.8 Hz, 4H), 7.52 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.53 (s, 3F); MS *m/z* (rel intensity) 339 (M^+, 89), 294 (100). Anal. Calcd for $C_{17}H_{16}NO_3F_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 60.25; H, 4.71; N, 4.03.

Ethyl 4-(4-Chlorophenyl)-2-methyl-6-trifluoromethylpyridine-3-carboxylate (5k): mp 43-44 °C (hexane); IR (Nuiol) ν = 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.09 (t, J = 7.2 Hz, 3H), 2.69 (s, 3H), 4.19 (q, J = 7.2 Hz, 2H), 7.34 and 7.44 (ABq, J = 8.3 Hz, 4H), 7.51 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.57 (s, 3F); MS *m/z* (rel intensity) 343 (M^+, 50), 298 (100). Anal. Calcd for $C_{16}H_{13}NO_2ClF_3$: C, 55.91; H, 3.81; N, 4.07. Found: C, 55.97; H, 3.78; N, 4.04.

Ethyl 4-(4-Fluorophenyl)-2-methyl-6-trifluoromethylpyridine-3-carboxylate (5l): mp 34-35 °C (hexane); IR (Nuiol) ν = 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.09 (t, J = 7.1 Hz, 3H), 2.98 (s, 3H), 4.18 (q, J = 7.1 Hz, 2H), 7.16 (dd, J = 8.8, 8.6 Hz, 2H), 7.39 (dd, J = 8.8, 5.1 Hz, 2H), 7.52 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = -33.90 (dd, J = 8.6, 5.1 Hz, 1F), 9.56 (s, 3F); MS *m/z* (rel intensity) 327 (M^+, 50), 282 (100). Anal. Calcd for $C_{16}H_{13}NO_2F_4$: C, 58.72; H, 4.00; N, 4.28. Found: C, 58.62; H, 3.96; N, 4.17.

Ethyl 2-Methyl-4-(4-nitrophenyl)-6-trifluoromethylpyridine-3-carboxylate (5m): mp 35-37 °C (hexane); IR (Nuiol) ν = 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.09 (t, J = 7.1 Hz, 3H), 2.73 (s, 3H), 4.19 (q, J = 7.1 Hz, 2H), 7.54 (s, 1H), 7.58 and 8.33 (ABq, J = 8.7 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ = 9.58 (s, 3F); MS *m/z* (rel intensity) 354 (M^+, 43), 309 (100). Anal. Calcd for $C_{16}H_{13}N_2O_4F_3$: C, 54.24; H, 3.70; N, 7.91. Found: C, 54.29; H, 3.75; N, 7.78.

Ethyl 2-Methyl-6-trifluoromethyl-4-(4-trifluoromethylphenyl)pyridine-3-carboxylate (5n): oil; IR (Neat) ν = 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.97 (t, J = 7.1 Hz, 3H), 2.64 (s, 3H), 4.09 (q, J = 7.1 Hz, 2H), 7.44 and 7.65 (ABq, J = 8.1 Hz, 4H), 7.46 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.54 (s, 3F), 14.95 (s,

3F); MS *m/z* (rel intensity) 377 (M^+, 37), 332 (100). Anal. Calcd for $C_{17}H_{13}NO_2F_6$: C, 54.12; H, 3.47; N, 3.71. Found: C, 54.26; H, 3.51; N, 3.58.

Ethyl 4-(2-Furyl)-2-methyl-6-trifluoromethylpyridine-3-carboxylate (5o): mp 30-32 °C (hexane); IR (Nuiol) ν = 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.38 (t, J = 7.1 Hz, 3H), 2.63 (s, 3H), 4.47 (q, J = 7.1 Hz, 2H), 6.55 (dd, J = 3.6, 1.7 Hz, 1H), 6.89 (dd, J = 3.6, 0.73 Hz, 1H), 7.57 (dd, J = 1.7, 0.73 Hz, 1H), 7.79 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.31 (s, 3F); MS *m/z* (rel intensity) 299 (M^+, 80), 271 (60), 254 (57), 243 (100). Anal. Calcd for $C_{14}H_{12}NO_3F_3$: C, 56.19; H, 4.04; N, 4.68. Found: C, 55.63; H, 3.93; N, 4.55.

Ethyl 2-Methyl-4-(2-thienyl)-6-trifluoromethylpyridine-3-carboxylate (5p): oil; IR (Neat) ν = 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.25 (t, J = 7.1 Hz, 3H), 2.66 (s, 3H), 4.33 (q, J = 7.1 Hz, 2H), 7.12 (dd, J = 5.0, 3.8 Hz, 1H), 7.30 (dd, J = 3.8, 1.1 Hz, 1H), 7.50 (dd, J = 5.0, 1.1 Hz, 1H), 7.63 (s, 1H); ^{19}F NMR ($CDCl_3$) δ = 9.50 (s, 3F); MS *m/z* (rel intensity) 315 (M^+, 74), 269 (100). Anal. Calcd for $C_{14}H_{12}NO_2F_3S$: C, 53.33; H, 3.84; N, 4.44. Found: C, 53.46; H, 3.86; N, 4.26.

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