A SIMPLE AND CONVENIENT SYNTHETIC METHOD FOR α-TRIFLUOROMETHYLPYRIDINES

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Abstract - β-Trifluoroacetylvinylamine (**1**) reacted easily with various active methylene compounds in the presence of trifluoroacetic acid under mild conditions to give α-trifluoromethylpyridines (**2**) in moderate to high yields.

Pyridine and the related derivatives constitute an important class of heterocyclic compounds and this ring system is found in a great number of natural products, for example alkaloids showing interesting biological activities.[1] Besides, recently much attention has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[2] Furthermore, in the course of our extensive studies on the electrophilic[3] and nucleophilic[4] substitutions at olefinic carbon atoms, it was found that β-trifluoroacetylvinylamine (**1**) can be easily prepared in two steps, trifluoroacetylation[3c] with trifluoroacetic anhydride and subsequent EtO-NH_2 exchange reaction[4a] with ammonia, starting from commercially available ethyl vinyl ether. This situation prompted us to utilize β-trifluoroacetylvinylamine (**1**) as a new and convenient building block for construction of fluorine-containing heterocyclic compounds, and we communicate here that α-trifluoromethylpyridines (**2**) can be very easily synthesized by the reaction of **1** constituting the N-C-C-C fragment in the pyridine ring system with active methylene compounds providing the two carbon unit.

In a typical experiment, to a solution of **1** (278 mg, 2.0 mmol) in benzene (10 mL) were added acetylacetone (240 mg, 2.4 mmol) and trifluoroacetic acid (274 mg, 2.4 mmol) and the mixture was stirred under reflux for 24 h. The reaction mixture was washed with aq. 20% Na_2CO_3 and dried (Na_2SO_4). After removal of the solvent, the residue was submitted to silica gel column chromatography to give selectively a 71% yield (290 mg) of α-trifluoromethylpyridine derivative (**2a**). The results are summarized and shown in Table 1. Quite similarly, such active methylene compounds as benzoylacetone, dibenzoylmethane, and methyl acetoacetate reacted with **1** in the presence of trifluoroacetic acid in refluxing benzene to afford the

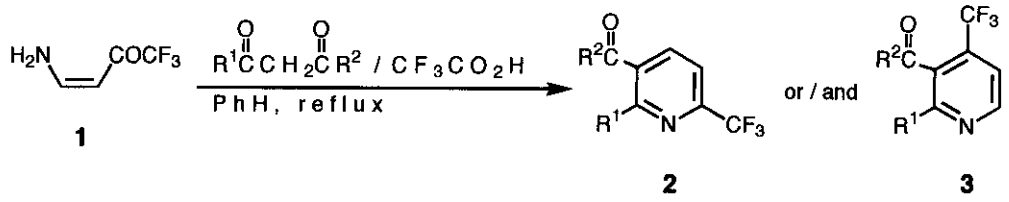
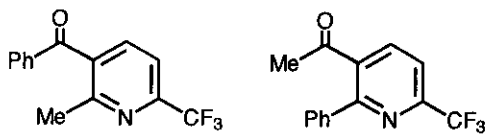


Table 1. Reaction of **1** with Active Methylene Compounds in the Presence of Trifluoroacetic Acid

Entry	R^1	R^2	$R^1COCH_2COR^2$ equiv.	CF_3CO_2H equiv.	Time(h)	Product	Yield (%)
1	Me	Me	1.2	1.2	24	**2a**	71
2	Me	Ph	1.0	1.0	24	**2b**	79
3	Ph	Ph	1.2	1.2	72	**2c**	40
4	CH_2CMe_2	CH_2	1.2	1.2	24	**2d / 3d**	32 / 16
5	CH_2CMe_2	CH_2	3.0	3.0	24	**2d / 3d**	23 / 31
6	Me	OMe	1.2	1.2	24	**2e**	88

unexpected α-trifluoromethylpyridines (**2b,c,e**) in 40-88% yields without any formation of expected γ-trifluoromethylpyridines (**3b,c,e**). However, not only α-trifluoromethylpyridine (**2d**: 32%) but also γ-trifluoromethylpyridine (**3d**: 16%) was produced in the reaction of **1** with dimedone. More interestingly, instead of unexpected α-CF_3-substituted pyridine (**2d**: 23%), its expected γ-CF_3-substituted regioisomer (**3d**: 31%) was obtained predominantly when treated with an excess (3 mole equiv.) of dimedone. The structures of compounds (**2a-e**, **3d**) were determined on the basis of their IR, ^{1}H- and ^{13}C-NMR spectra, together with elemental analyses.[5] In particular, ^{1}H- and ^{13}C-NMR spectra provided diagnostic information for the structural distinction between α-trifluoromethylpyridine (**2**) and its regioisomeric form γ-trifluoromethylpyridine (**3**). In ^{1}H-NMR spectra, the chemical shift of H-α in **3d** appeared in the downfield with respect to that of H-γ in **2a,d,e** by *ca.* 0.5-0.9 ppm and vicinal H_α-H_β coupling constant (5 Hz) in **3d** was much smaller than H_β-H_γ one (8 Hz) in **2a,d,e**. Moreover, in ^{13}C-NMR spectra of α-trifluoromethylpyridines (**2a-e**), there appeared two characteristic signals for C-α bearing a trifluoromethyl group appeared at 148.7-151.3 ppm as quartet (J_{CF}=34.2 or 35.4 Hz) and unsubstituted C-γ at 136.4-140.1 ppm as doublet. In contrast to this, ^{13}C-NMR spectrum of γ-trifluoromethylpyridine (**3d**) showed a doublet for unsubstituted C-α at 160.8 ppm and a quartet (J_{CF}=35.4 Hz) for C-γ bearing a trifluoromethyl group at 137.5 ppm. The clear structural distinction between **2b** and **2b'** was also made by judging from the chemical shifts of $\underline{C}H_3$-α' attached to the pyridine ring. In **2b**, its chemical shift (23.2 ppm) was much more similar to that (24.4 or 24.7 ppm) of $\underline{C}H_3$-α' in **2a,e** than that (29.5 ppm) of $CO\underline{C}H_3$-β' in **2a**.



2b **2b'**

Thus, the present synthetic method provides a simple and convenient access to pyridines having a trifluoromethyl group at the α-position which are not easily obtained by other methods. Further utilization

of **1** as a useful synthetic block and investigations from the mechanistic standpoint of view are now in progress in our laboratory.

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5. **2a:** bp 70 ℃/3 mmHg (oven temperature); IR (film): 1693, 1579 cm^{-1}; ^{1}H-NMR (δ , $CDCl_3$): 8.08 (d, 1H, J=8 Hz, H- γ), 7.60 (d, 1H, J=8, H- β), 2.77 (s, 3H, $COCH_3$), 2.63 (s, 3H, CH_3- α); ^{13}C-NMR (δ , $CDCl_3$): 199.8 (s), 158.9 (s), 149.0 (q, J_{CF}=35.4 Hz), 138.1 (d), 135.9 (s), 121.5 (q, J_{CF}=274.7 Hz), 118.0 (dq, J_{CF}=2.4 Hz), 29.5 (q), 24.4 (q). Anal. Calcd for $C_9H_8NOF_3$: C, 53.21; H, 3.97; N, 6.89. Found: C, 53.29; H, 3.87; N, 6.92. **2b:** bp 145℃/3 mmHg (oven temperature);

IR (film): 1665, 1594, 1576 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$): 7.87-7.20 (m, 7H, H- β, H- γ, C_6H_5), 2.57 (s, 3H, CH_3- α); ^{13}C-NMR (δ, $CDCl_3$): 195.6 (s), 157.6 (s), 148.7 (q, J_{CF}=34.2 Hz), 137.1 (d), 137.1 (s), 136.5 (s), 134.3 (d), 130.1 (d), 129.0 (d), 121.4 (q, J_{CF}=274.7 Hz), 117.3 (dq, J_{CF}=2.4 Hz), 23.2 (q). Anal. Calcd for $C_{14}H_{10}NOF_3$: C, 63.40; H, 3.80; N, 5.28. Found: C, 63.54; H, 3.86; N, 5.34. **2c:** mp 105-106 ℃ (recrystallized from hexane); IR (KBr): 1658, 1593, 1575 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$): 7.90-7.03 (m, 12H, H- β, H- γ, $2C_6H_5$); ^{13}C-NMR (δ, $CDCl_3$): 195.9 (s), 157.6 (s), 148.8 (q, J_{CF}=34.2 Hz), 138.6 (d), 137.9 (s), 137.0 (s), 136.0 (s), 133.9 (d), 129.8 (d), 129.5 (d), 129.4 (d), 128.7 (d), 128.5 (d), 121.4 (q, J_{CF}=274.7 Hz), 118.3 (dq, J_{CF}=2.4 Hz). Anal. Calcd for $C_{19}H_{12}NOF_3$: C, 69.72; H, 3.70; N, 4.28. Found: C, 69.84; H, 3.93; N, 3.94. **2d:** bp 105℃/3 mmHg (oven temperature); IR (film): 1695, 1660, 1593 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$): 8.44 (d, 1H, J=8 Hz, H- γ), 7.69 (d, 1H, J=8, H- β), 3.15 (s, 2H, CH_2CO), 2.63 (s, 2H, CH_2), 1.16 (s, 6H, $2CH_3$); ^{13}C-NMR (δ, $CDCl_3$): 196.7 (s), 162.9 (s), 151.3 (q, J_{CF}=34.2 Hz), 136.4 (d), 129.2 (s), 121.2 (q, J_{CF}=274.7 Hz), 118.9 (dq, J_{CF}=2.4 Hz), 52.0 (t), 46.2 (t), 32.9 (s), 28.2 (q). Anal. Calcd for $C_{12}H_{12}NOF_3$: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.35; H, 4.93; N, 5.71. **2e:** bp 75 ℃/3 mmHg (oven temperature); IR (film): 1729, 1585 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$): 8.32 (d, 1H, J=8 Hz, H- γ), 7.56 (d, 1H, J=8, H- β), 3.94 (s, 3H, CO_2CH_3), 2.87 (s, 3H, CH_3- α); ^{13}C-NMR (δ, $CDCl_3$): 166.0 (s), 161.0 (s), 149.8 (q, J_{CF}=34.2 Hz), 140.1 (d), 128.3 (s), 121.5 (q, J_{CF}=274.7 Hz), 117.8 (dq, J_{CF}=2.4 Hz), 52.7 (q), 24.7 (q). Anal. Calcd for $C_9H_8NO_2F_3$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.47; H, 3.56; N, 6.36. **3d:** mp 53-54 ℃ (recrystallized from hexane); IR (KBr): 1705, 1570 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$): 8.95 (d, 1H, J=5 Hz, H- α), 7.68 (d, 1H, J=5, H- β), 3.20 (s, 2H, CH_2CO), 2.67 (s, 2H, CH_2), 1.17 (s, 6H, $2CH_3$); ^{13}C-NMR (δ, $CDCl_3$): 195.4 (s), 164.0 (s), 160.8 (d),137.5 (q, J_{CF}=35.4 Hz), 125.4 (s), 122.3 (q, J_{CF}=274.7 Hz), 120.3 (dq, J_{CF}=6.1 Hz), 53.3 (t), 46.8 (t), 32.6 (s), 28.1 (q). Anal. Calcd for $C_{12}H_{12}NOF_3$: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.18; H, 4.77; N, 6.03.

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