A FACILE AND CONVENIENT SYNTHETIC METHOD FOR 3-TRIFLUOROACETYL-PYRROLES

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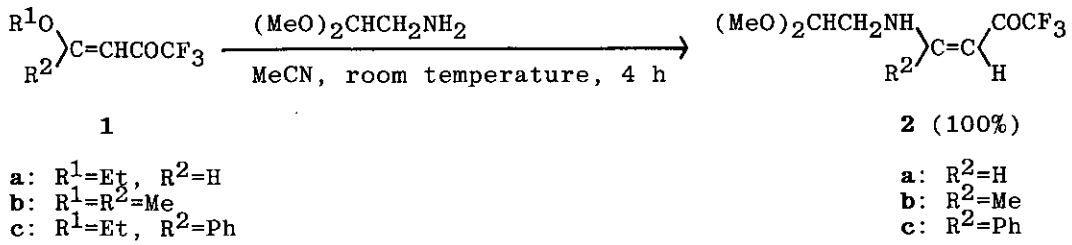
Abstract - 3-Trifluoroacetylpyrroles are easily obtained in excellent yields by oxygen-nitrogen exchange reaction of β-trifluoroacetylvinyl ethers with 2,2-dimethoxyethylamine and subsequent cyclodehydration of the products.

A great deal of effort has been directed toward developing new methods for constructing the pyrrole ring system, because it is found in many naturally occurring compounds and many of them show interesting biological activities.[1] Although 2-acylpyrroles can be easily prepared from pyrrole by direct acylation reaction, access to 3-acylpyrroles is fairly limited.[2] In the electrophilic substitution of N-substituted pyrroles with trifluoroacetic anhydride, trifluoroacetylation occurred exclusively or predominantly at the 2-position[3-5] except for the use of very bulky group on nitrogen atom such as tert-butyl,[5] 1-adamantyl,[5] trityl,[6] and triisopropylsilyl[7] groups. On the other hand, during our investigations on nucleophilic substitutions at olefinic carbon atoms,[8-10] it was found that β-trifluoroacetylvinyl ethers react readily with various amines under mild conditions to give the corresponding β-trifluoroacetylenamines in high yields.[8] In this paper, we would like to report a very facile and convenient synthetic method for 3-trifluoroacetylpyrroles by making use of nucleophilic oxygen-nitrogen exchange reaction of β-trifluoroacetylvinyl ethers with 2,2-dimethoxyethylamine.

Nucleophilic oxygen-nitrogen exchange reaction of β-trifluoroacetylvinyl ethers (**1a-c**), which can be easily prepared by trifluoroacetylation of



1

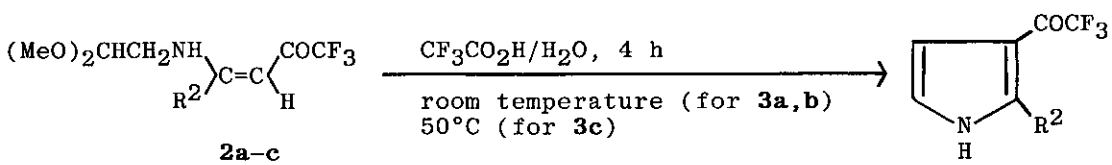
a: R^1=Et, R^2=H
b: R^1=R^2=Me
c: R^1=Et, R^2=Ph

2 (100%)

a: R^2=H
b: R^2=Me
c: R^2=Ph

Scheme 1

ethyl vinyl ether,[11] acetone dimethyl acetal,[12] and acetophenone diethyl acetal,[12] with 2,2-dimethoxyethylamine, proceeded readily at room temperature for 4 h to give the corresponding β-trifluoroacetylenamines (**2a-c**) quantitatively (Scheme 1). The stereochemistry of compounds (**2a-c**) was confirmed by ^{1}H-nmr spectra. The small magnitude of the coupling constant $J_{CH=CH}$ (7 Hz) and/or the much deshielded peak of amino protons (9.58-11.38 ppm) due to hydrogen bonding between NH and C=O indicates Z configuration.[13] The desired 3-trifluoroacetylpyrroles (**3a-c**) could be synthesized in 87-100% yields easily in one-pot, by hydrolysis of the acetal moiety



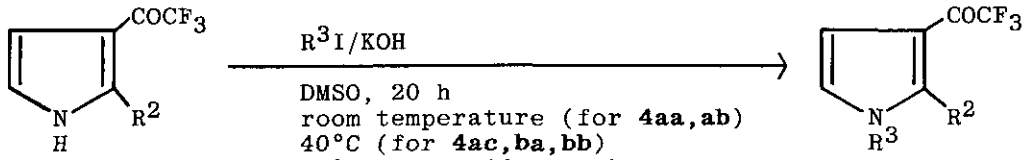
2a-c

3 (87-100%)

a: R^2=H
b: R^2=Me
c: R^2=Ph

Scheme 2

and subsequent cyclodehydration of β-trifluoroacetylenamines (**2a-c**) in trifluoroacetic acid containing a small amount of water (Scheme 2).[14]



3a–c

4 (92–100%)

aa: R^2=H, R^3=Me
ab: R^2=H, R^3=Et
ac: R^2=H, R^3=i-Pr
ba: R^2=R^3=Me
bb: R^2=Me, R^3=Et
ca: R^2=Ph, R^3=Me
cb: R^2=Ph, R^3=Et

Scheme 3

N-Alkylation of **3a–c** was also successfully performed by treatment of them with alkyl iodides in the presence of potassium hydroxide in dimethyl sulfoxide to afford the corresponding 1-alkyl-3-trifluoroacetylpyrroles (**4aa–cb**) in high yields (Scheme 3).[15]

In conclusion, nucleophilic oxygen-nitrogen exchange reaction of **1** with 2,2-dimethoxyethylamine, followed by cyclodehydration provides a new extremely simple and efficient approach to 3-trifluoroacetylpyrroles which are not easily accessible by other methods.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. Ir spectra were recorded on a Hitachi EPI-G3 spectrophotometer. ^{1}H-Nmr spectra were obtained with a JEOL PMX-60SI spectrometer using $CDCl_3$ as a solvent. All chemical shifts are reported in ppm downfield from internal tetrametylsilane; coupling constants (J) are given in Hz. Elemental analyses were performed by the Microanalyses Center of Kyoto University. All reagents and solvents were obtained commercially, dried over molecular sieves, and used without further purification.

Oxygen-Nitrogen Exchange Reaction of β-Trifluoroacetylvinyl Ethers (1a-c) with 2,2-Dimethoxyethylamine; General Procedure: To a solution of **1a**,[11] **1b**,[12] or **1c**[12] (10 mmol) in MeCN (40 ml) was added 2,2-dimethoxyethylamine (1.10 g, 10.5 mmol). The solution was stirred at room temperature for 4 h and the solvent was removed under reduced pressure to give **2a-c**.

1,1,1-Trifluoro-4-(2,2-dimethoxyethylamino)-3-buten-2-one (2a): yield: 2.27 g (100%); bp 150 °C/6 mmHg; ir (film) 3275, 1653, 1590 cm^{-1}; ^{1}H-nmr 10.42-9.58 (1H, br, NH), 7.02 (1H, dd, J=7, 10, NCH=), 5.33 (1H, d, J=7, =CHCO), 4.38 (1H, t, J=5, C$\underline{H}$C$\underline{H}_2$N), 3.26-3.45 (8H, m, (C$\underline{H}_3$O)$_2$CHC$\underline{H}_2$). Anal. Calcd for $C_8H_{12}NO_3F_3$: C, 42.30; H, 5.32; N, 6.17. Found: C, 42.40; H, 5.41; N, 6.21.

1,1,1-Trifluoro-4-(2,2-dimethoxyethylamino)-3-penten-2-one (2b): yield: 2.41 g (100%); bp 55 °C/4 mmHg; ir (film) 3210, 1622, 1590 cm^{-1}; ^{1}H-nmr 11.38-10.73 (1H, br, NH), 5.25 (1H, s, =CHCO), 4.42 (1H, t, J=5, C$\underline{H}$C$\underline{H}_2$N), 3.52-3.38 (8H, m, (C$\underline{H}_3$O)$_2$CHC$\underline{H}_2$), 2.07 (3H, s, CH_3C=). Anal. Calcd for $C_9H_{14}NO_3F_3$: C, 44.82; H, 5.85; N, 5.81; F, 23.63. Found: C, 44.39; H, 5.87; N, 5.83; F, 23.93.

1,1,1-Trifluoro-4-(2,2-dimethoxyethylamino)-4-phenyl-3-buten-2-one (2c): yield: 3.03 g (100%); bp 120 °C/4 mmHg; ir (film) 3220, 1623, 1603, 1585 cm^{-1}; ^{1}H-nmr (CCl_4) 11.23-10.77 (1H, br, NH), 7.32 (5H, s, C_6H_5), 5.27 (1H, s, =CHCO), 4.32 (1H, t, J=5, C$\underline{H}$C$\underline{H}_2$N), 3.35-3.17 (8H, m, (C$\underline{H}_3$O)$_2$CHC$\underline{H}_2$). Anal. Calcd for $C_{14}H_{16}NO_3F_3$: C, 55.44; H, 5.32; N, 4.62. Found: C, 55.16; H, 5.23; N, 4.59.

Synthesis of 3-Trifluoroacetylpyrroles (3a-c) from β-Trifluoroacetylenamines (2a-c); General Procedure (See Scheme 2): A solution of **2a-c** (2 mmol) in trifluoroacetic acid (2 ml) containing a small amount of water was stirred at room temperature or at 50 °C for 4 h. The mixture was washed with aq. 10% Na_2CO_3, extracted with CH_2Cl_2, and dried (Na_2SO_4). Evaporation of the solvent afforded **3a-c**.

3-Trifluoroacetylpyrrole (3a): yield: 285 mg (87%); mp 110-111 °C ($CHCl_3$)

(lit.[7] mp 111-112 °C).

3-Trifluoroacetyl-2-methylpyrrole (3b): yield: 355 mg (100%); mp 108-109 °C (hexane/$CHCl_3$); ir (KBr) 3330, 1650 cm^{-1}; ^{1}H-nmr 10.28-8.35 (1H, br, NH), 6.64-6.56 (2H, m, H-4, -5), 2.58 (3H, s, CH_3). Anal. Calcd for $C_7H_6NOF_3$: C, 47.47: H, 3.41; N, 7.91; F, 32.18. Found: C, 47.26; H, 3.34; N, 7.93; F, 31.93.

3-Trifluoroacetyl-2-phenylpyrrole (3c): yield: 478 mg (100%); mp 123-124 °C ($CHCl_3$); ir (KBr) 3345, 1668 cm^{-1}; ^{1}H-nmr 10.20-7.90 (1H, br, NH), 7.67-7.22 (5H, m, C_6H_5), 6.88-6.72 (2H, m, H-4, -5). Anal. Calcd for $C_{12}H_8NOF_3$: C, 60.26; H, 3.37; N, 5.86; F, 23.83. Found: C, 60.20; H, 3.22; N, 5.91; F, 24.05.

N-Alkylation of 3-Trifluoroacetylpyrroles (3a-c); General Procedure (See Scheme 3): Powdered KOH (135 mg, 2.4 mmol) and **3a-c** (2 mmol) were dissolved in DMSO (16 ml). To this solution was added methyl (20 mmol), ethyl (6 mmol), or isopropyl (6 mmol) iodide, and the mixture was stirred at room temperature to 70 °C for 20 h to 4 days. The mixture was washed with water, extracted with CH_2Cl_2, and dried (Na_2SO_4). The solvent was evaporated to give **4aa-cb**. In the synthesis of **4ca** 8.52 g (60 mmol) of methyl iodide was used to 2 mmol of **3c**.

3-Trifluoroacetyl-1-methylpyrrole (4aa): yield: 338 mg (95%); bp 60 °C/5 mmHg; ir (film) 1692 cm^{-1}; ^{1}H-nmr 7.35 (1H, br s, H-2), 6.75-6.48 (2H, m, H-4, -5), 3.68 (3H, s, CH_3). Anal. Calcd for $C_7H_6NOF_3$: C, 47.47; H, 3.41; N, 7.91; F, 32.18. Found: C, 47.32; H, 3.52; N, 8.01; F, 32.10.

1-Ethyl-3-trifluoroacetylpyrrole (4ab): yield: 353 mg (92%); bp 85 °C/4 mmHg; ir (film) 1690 cm^{-1}; ^{1}H-nmr 7.42 (1H, br s, H-2), 6.65-6.62 (2H, m, H-4, -5), 3.73 (2H, q, J=7, CH_2), 1.45 (3H, t, J=7, CH_3). Anal. Calcd for $C_8H_8NOF_3$: C, 50.27; H, 4.22; N, 7.33. Found: C, 50.44; H, 4.11;, N, 7.35.

3-Trifluoroacetyl-1-isopropylpyrrole (4ac): yield: 404 mg (98%); bp 85 °C/5 mmHg; ir (film) 1685 cm^{-1}; ^{1}H-nmr 7.44 (1H, br s, H-2), 6.66-6.63

(2H, m, H-4, -5), 4.23 (1H, hp, J=7, C<u>H</u>$(CH_3)_2$), 1.48 (6H, d, J=7, CH(C<u>H</u>$_3)_2$). Anal. Calcd for $C_9H_{10}NOF_3$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.93; H, 5.00; N, 7.00.

3-Trifluoroacetyl-1,2-dimethylpyrrole (4ba): yield: 381 mg (100%); mp 68-69 °C (hexane); ir (KBr) 1668 cm^{-1}; ^{1}H-nmr 6.62-6.40 (2H, m, H-4, -5), 3.51 (3H, s, NCH_3), 2.51 (3H, s, CCH_3). Anal. Calcd for $C_8H_8NOF_3$: C, 50.27; H, 4.22; N, 7.33; F, 29.82. Found: C, 49.99; H, 4.00; N, 7.08; F, 29.80.

1-Ethyl-3-trifluoroacetyl-2-methylpyrrole (4bb): yield: 413 mg (100%); bp 70 °C/5 mmHg; ir (film) 1675 cm^{-1}; ^{1}H-nmr 6.52 (2H, s, H-4, -5), 3.88 (2H, q, J=7, C<u>H</u>$_2$$CH_3$), 2.55 (3H, s, CH_3-2), 1.35 (3H, t, J=7, CH_2C<u>H</u>$_3$). Anal. Calcd for $C_9H_{10}NOF_3$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.97; H, 4.85; N, 6.91.

3-Trifluoroacetyl-1-methyl-2-phenylpyrrole (4ca): yield: 510 mg (100%); mp 75-76 °C (benzene); ir (KBr) 1683 cm^{-1}; ^{1}H-nmr 7.40-7.01 (5H, m, C_6H_5), 6.67-6.48 (2H, m, H-4, -5), 3.37 (3H, s, CH_3). Anal. Calcd for $C_{13}H_{10}NOF_3$: C, 61.66; H, 3.98; N, 5.53. Found: C, 61.53; H, 3.93; N, 5.60.

1-Ethyl-3-trifluoroacetyl-2-phenylpyrrole (4cb): yield: 532 mg (100%); mp 101-102 °C (hexane); ir (KBr) 1685 cm^{-1}; ^{1}H-nmr 7.47-7.18 (5H, m, C_6H_5), 6.72 (2H, br s, H-4, -5), 3.75 (2H, q, J=7, C<u>H</u>$_2$$CH_3$), 1.25 (3H, t, J=7, CH_2C<u>H</u>$_3$). Anal. Calcd for $C_{14}H_{12}NOF_3$: C, 62.92; H, 4.53; N, 5.24. Found: C, 62.79; H, 4.40; N, 5.29.

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13. The configurations of compounds (**1a-c**) are as follows: **1a**, E; **1b**, a single stereoisomer of E or Z (not determined); **1c**, E/Z (ca. 5:1).
14. Very recently **3a** was synthesized in 49% yield (based on N-triisopropylsilylpyrrole) by desilylation of 3-trifluoroacetyl-1-triisopropylsilylpyrrole obtained by trifluoroacetylation of N-triisopropylsilylpyrrole. See ref. 7.
15. In trifluoroacetylation of N-isopropylpyrrole, **4ac** was produced as a minor product (12% yield) with a main product of 2-trifluoroacetyl-1-isopropylpyrrole (68% yield). See ref. 5.

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