FACILE SYNTHETIC METHODS FOR 3- AND 5-TRIFLUOROMETHYL-4-TRIFLUOROACETYL-PYRAZOLES AND THEIR CONVERSION INTO PYRAZOLE-4-CARBOXYLIC ACIDS

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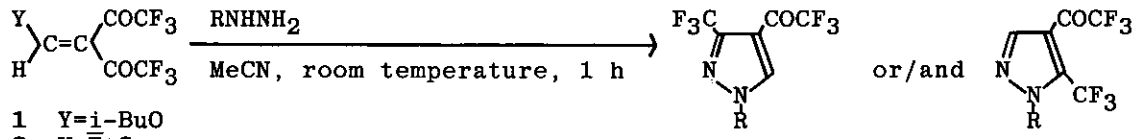
Abstract - 3- and 5-Trifluoromethyl-4-trifluoroacetylpyrazoles (4 and 5) were easily synthesized in excellent yields by reaction of β,β-bis(trifluoroacetyl)vinyl ethers 1, sulfides 2, and -amines 3 with hydrazines. Hydrolysis of these compounds (4 and 5) with aqueous potassium hydroxide gave the corresponding pyrazole-4-carboxylic acids (6 and 7) in high yields.

In the course of our extensive investigations on the nucleophilic substitutions at olefinic carbon atoms,[1-6] it was found that β,β-bis(trifluoroacetyl)vinyl i-butyl ether 1 readily reacts with various thiols and amines under very mild conditions to give the corresponding O-S and O-N exchanged products (e.g., 2 and 3) in high yields.[6] As an extension of this work, we used this type of nucleophilic exchange reaction and subsequent cyclodehydration with bifunctional N-nucleophiles such as hydrazines to prepare 3- and 5-trifluoromethyl-4-trifluoroacetylpyrazoles (4 and 5) which are hardly obtainable by other routes. The conversion of the products (4 and 5) into 3- and 5-trifluoromethylpyrazole-4-carboxylic acids (6 and 7) by alkaline hydrolysis was also studied. Recently, the development of new methodologies for the synthesis of various fluorine-containing heterocycles has received a growing interest, since many kinds of these compounds are now widely recognized as important organic materials exhibiting interesting functionalities for use in medicinal and agricultural science.[7-9] Besides, pyrazolecarboxylic acids have been very useful intermediates for fine chemicals, and development of effective synthetic methods for these compounds is nowadays much desirable.[10,11]

Ether 1, which is readily prepared from i-butyl vinyl ether and trifluoroacetic anhy-



1 Y=i-BuO
2 Y=EtS
3 Y=Me_2N

4a-c **5b-d**

Scheme 1

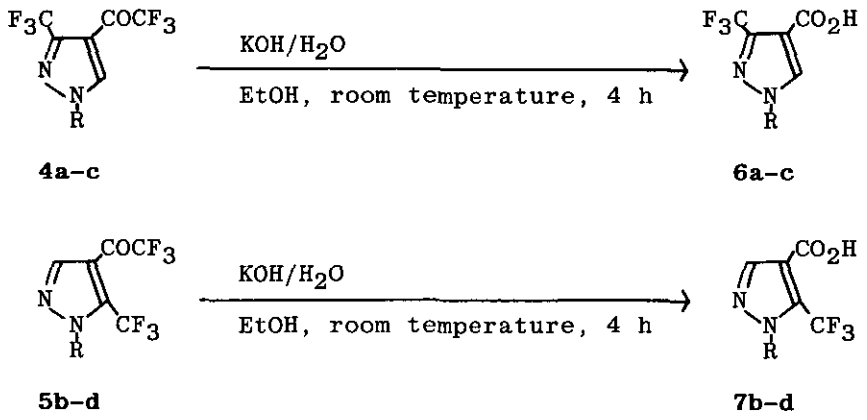
Table 1. Synthesis of 3- and 5-Trifluoromethyl-4-trifluoroacetylpyrazoles

Entry	Substrate	Hydrazine, R	Product	Yield (%)[a]
1	1	Me	**4a**	73
2	2	Me	**4a**	93
3	3	Me	**4a**	97
4	1	t-Bu[b]	**4b / 5b**	10 / 20
5	2	t-Bu[b]	**5b**	94
6	3	t-Bu[b]	**5b**	94
7	1	Ph	**4c / 5c**	12 / 62
8	2	Ph	**4c / 5c**	20 / 80
9	3	Ph	**4c / 5c**	5 / 95
10	1	p-$NO_2C_6H_4$	**5d**	75

a) Yield of isolated products. b) t-Butylhydrazine hydrochloride was used in the presence of triethylamine.

dride,[12] reacted quite easily with methylhydrazine at room temperature for 1 h to give only 3-trifluoromethylpyrazole **4a** in 73% yield (Scheme 1 and Table 1). The similar reactions of sulfide 2 and amine 3 also afforded **4a** as a sole product in 93 and 97% yields, respectively. In contrast, the reaction of sulfide 2 and amine 3 with t-butylhydrazine hydrochloride in the presence of triethylamine yielded exclusively 5-trifluoromethylpyrazole **5b** in high yields without formation of any detectable amounts of 3-trifluoromethylpyrazole **4b**. However, this regioselectivity was lost and the yields went down in the reaction of ether **1**, where a mixture of **5b** (20%) and **4b** (10%) was obtained together with decomposition products. The reactions of **1-3** with phenylhydrazine resulted in preferential formation of 5-trifluoromethylpyrazole **5c** in 62-95% yields, with formation of isomeric 3-trifluoromethylpyrazole **4c** in 5-20% yields. These isomeric pyrazoles (**4c** and **5c**) were separated and isolated in pure state by careful column chromatography on silica gel. Ether **1** reacted easily with p-nitrophenylhydrazine to provide exclusively 5-trifluoromethylpyrazole **5d** in 75% yield and none of the possible regioisomer was found.

The hydrolysis of 4-trifluoroacetylpyrazoles (**4a-c** and **5b-d**) with saturated aqueous potas-



Scheme 2

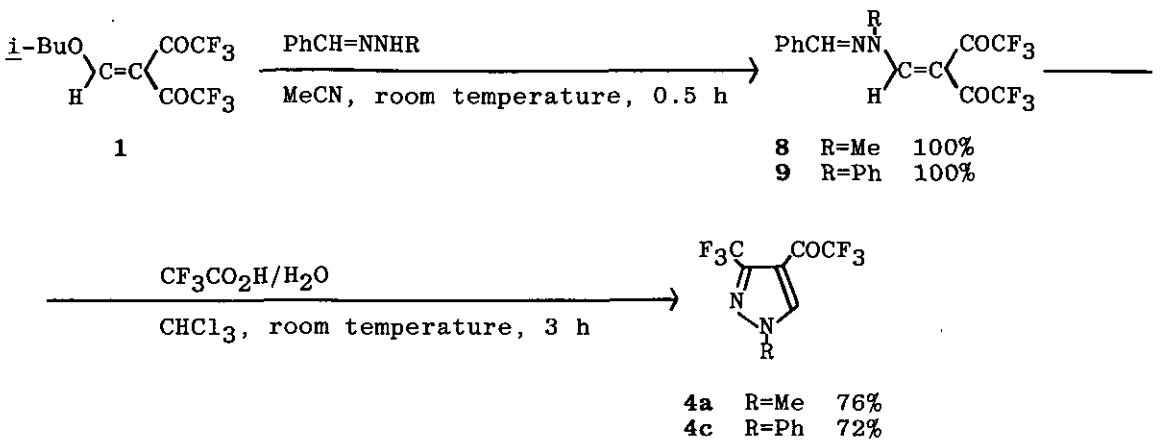
Table 2. Synthesis of 3- and 5-Trifluoromethylpyrazole-4-carboxylic Acids

Entry	Substrate	Product	Yield (%)[a]
1	**4a**	**6a**	93
2	**4b**	**6b**	100
3	**4c**	**6c**	100
4	**5b**	**7b**	84
5	**5c**	**7c**	85
6	**5d**	**7d**	100

a) Yield of isolated products.

sium hydroxide was performed in ethanol as solvent at room temperature for 4 h to give the corresponding pyrazole-4-carboxylic acids (**6a-c** and **7b-d**) in 84-100% yields (Scheme 2 and Table 2).

The structures of compounds **4-7** were determined on the basis of their ^{1}H-nmr, ir, and elemental analyses. In paticular, the structural distinction between 3-trifluoromethylpyrazoles (**4a** and **4c**) and 5-trifluoromethylpyrazole **5c** was confirmed by comparison with authentic samples which were prepared independently as follows (Scheme 3). Treatment of ether **1** with benzaldehyde methyl- and phenylhydrazones at room temperature for 0.5 h gave the corresponding *O-N exchanged products* (**8** and **9**) *in quantitative yields*. Hydrolysis of azomethine moiety and subsequent cyclodehydration were performed in one-pot by merely mixing hydrazones (**8** and **9**) and trifluoroacetic acid containing a small amount of water in chloroform at room temperature for 3 h to afford 3-trifluoromethylpyrazoles (**4a** and **4c**) in 72-76% yields. Both ^{1}H-nmr and ir spectra of the resulting pyrazoles (**4a** and **4c**) were



Scheme 3

in good accordance with those of the samples obtained directly from **1-3** and the corresponding hydrazines. Coincidence of the two **4a**'s obtained independently was ascertained by converting them further into pyrazole-4-carboxylic acid **6a** and by mixed melting point. Likewise, structure of **4c** was confirmed. Since the structure of 3-trifluoromethylpyrazole **4c** was established as above, the other pyrazole **5c** should be the isomeric 5-trifluoromethylated pyrazole. Although the alternative syntheses of 3-trifluoromethylpyrazoles (**4b** and **4d**) from **1-3** with benzaldehyde t-butyl- and p-nitrophenylhydrazones failed, the clear structural distinction between the two regioisomers was made by judging from the chemical shifts for the ring protons of the pyrazoles. The chemical shifts of H-5 in **4b** and **4c** appeared downfield with respect to those of H-3 in **5b** and **5c** by ca. 0.3 ppm. In the case of **5d**, the chemical shift of its H-3 (8.20 ppm) was much more similar to that of H-3 (8.12 ppm) in **5c** than that of H-5 (8.39 ppm) in **4c**.

In conclusion, nucleophilic O-N, S-N, and N-N exchange reactions of **1-3** with hydrazines, followed by cyclodehydration provide a facile synthetic method for 3- and 5-trifluoromethyl-4-trifluoroacetylpyrazoles, which are easily converted into 3- and 5-trifluoromethylpyrazole-4-carboxylic acids.

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 JEOL PMX 60SI spectrometer using $CDCl_3$ as a solvent unless otherwise indicated. All chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants (J) are given in Hz. Elemental analyses were performed by the Microanalyses Center of Kyoto University. Chromatographic separations were carried out on silica gel column (Wakogel C-200; 100-200 mesh). Benzaldehyde methyl- and phenylhydrazones were prepared by condensation of benzaldehyde with methyl- and phenylhydrazines. All other reagents and solvents were obtained commercially, dried over molecular sieves, and used without further purification.

Reaction of β,β-Bis(trifluoroacetyl)vinyl Ether 1, Sulfide 2, and Amine 3 with Hydrazines; General Procedure: Method A (for entries 1-3 in Table 1): To a solution of **1**,[12] **2**,[6] or **3**[6] (2 mmol) in MeCN (10 ml) was added methylhydrazine (2 mmol). The solution was stirred at room temperature for 1 h, then evaporated under reduced pressure to give **4a**. **Method B** (for entries 4-6 in Table 1): To a suspension of tert-butylhydrazine hydrochloride (5 mmol) and triethylamine (0.51 g, 5 mmol) in MeCN (20 ml) was added **1**, **2**, or **3** (5 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and CH_2Cl_2 (100 ml) was added to the residue. This solution was washed with H_2O (300 ml) and dried (Na_2SO_4). The solvent was evaporated, and the crude product was chromatographed using hexane/benzene (1:1) for **4b** and hexane/benzene (4:1) for **5b** as eluent. **Method C** (for entries 7-10 in Table 1): To a solution of **1**, **2**, or **3** (2 mmol) in MeCN (10 ml) was added phenyl- or p-nitrophenylhydrazine (2 mmol) and the whole mixture was stirred at room temperature for 1 h. The resulting solution was evaporated and the crude product was chromatographed using hexane/benzene (1:1) for **4c**, hexane/benzene (2:1) for **5c**, and benzene for **5d** as eluent.

4-Trifluoroacetyl-3-trifluoromethyl-1-methylpyrazole 4a: bp 100 °C/1 mmHg; ir (film) 1720 cm^{-1}; ^1H-nmr 8.03 (1H, s, H-5), 4.03 (3H, s, CH_3). Anal. Calcd for $C_7H_4N_2OF_6$: C, 34.16; H, 1.64; N, 11.38; F, 46.32. Found: C, 34.34; H, 1.70; N, 11.46; F, 46.11.

1-(t-Butyl)-4-trifluoroacetyl-3-trifluoromethylpyrazole 4b: mp 41-42 °C (hexane); ir (KBr) 1723 cm^{-1}; ^1H-nmr 8.13 (1H, s, H-5), 1.66 (9H, s, $C(CH_3)_3$). Anal. Calcd for $C_{10}H_{10}N_2OF_6$: C, 41.68; H, 3.50; N, 9.72; F, 39.55. Found: C, 41.58; H, 3.44; N, 9.78; F, 39.70.

4-Trifluoroacetyl-3-trifluoromethyl-1-phenylpyrazole 4c: mp 88-89 °C (benzene); ir (KBr)

1723 cm^{-1}; ^{1}H-nmr 8.39 (1H, s, H-5), 7.72-7.32 (5H, s, C_6H_5). Anal. Calcd for $C_{12}H_6N_2OF_6$: C, 46.77; H, 1.96; N, 9.09; F, 36.99. Found: C, 46.90; H, 1.96; N, 9.35; F, 36.97.

1-(t-Butyl)-4-trifluoroacetyl-5-trifluoromethylpyrazole 5b: bp 50 °C/4 mmHg; ir (film) 1737 cm^{-1}; ^{1}H-nmr 7.83 (1H, s, H-3), 1.73 (9H, s, $C(CH_3)_3$). Anal. Calcd for $C_{10}H_{10}N_2OF_6$: C, 41.68; H, 3.50; N, 9.72; F, 39.55. Found: C, 41.73; H, 3.47; N, 9.87; F, 39.26.

4-Trifluoroacetyl-5-trifluoromethyl-1-phenylpyrazole 5c: bp 80 °C/1 mmHg; ir (film) 1724 cm^{-1}; ^{1}H-nmr 8.12 (1H, s, H-3), 7.42 (5H, s, C_6H_5). Anal. Calcd for $C_{12}H_6N_2OF_6$: C, 46.77; H, 1.96; N, 9.09. Found: C, 46.80; H, 1.94; N, 9.37.

4-Trifluoroacetyl-5-trifluoromethyl-1-(p-nitrophenyl)pyrazole 5d: mp 84-85 °C (benzene); ir (KBr) 1726 cm^{-1}; ^{1}H-nmr 8.33 (2H, d, J=9, C_6H_4), 8.20 (1H, s, H-3), 7.60 (2H, d, J=9, C_6H_4). Anal. Calcd for $C_{12}H_5N_3O_3F_6$: C, 40.81; H, 1.43; N, 11.90; F, 32.27. Found: C, 40.82; H, 1.36; N, 12.03; F, 32.33.

Conversion of 4-Trifluoroacetylpyrazoles (4 and 5) into Pyrazole-4-carboxylic Acids (6 and 7); General Procedure: To a stirred solution of 4 or 5 (1 mmol) in EtOH (4 ml) was added saturated aqueous solution of KOH (2 ml) and stirring was continued at room temperature for 4 h. The basic solution was acidified with 2N HCl (20 ml) in an ice bath. Most of the solvent was removed under reduced pressure and the resulting mixture was diluted with CH_2Cl_2 (50 ml), and dried (Na_2SO_4). Evaporation of the solvent gave pyrazole-4-carboxylic acids (6 or 7).

3-Trifluoromethyl-1-methylpyrazole-4-carboxylic Acid 6a: mp 199-200 °C ($CHCl_3$); ir (KBr) 3575-2175, 1731 cm^{-1}; ^{1}H-nmr ($CD_3CN/CDCl_3$) 8.00 (1H, s, H-5), 6.17 (1H, br s, OH), 3.88 (3H, s, CH_3). Anal. Calcd for $C_6H_5N_2O_2F_3$: C, 37.13; H, 2.60; N, 14.43; F, 29.36. Found: C, 37.11; H, 2.53; N, 14.38; F, 29.15.

1-(t-Butyl)-3-trifluoromethylpyrazole-4-carboxylic Acid 6b: mp 163-164 °C (benzene); ir (KBr) 3700-2100, 1711 cm^{-1}; ^{1}H-nmr 8.27-7.57 (1H, br, OH), 8.12 (1H, s, H-5), 1.62 (9H, s, $C(CH_3)_3$). Anal. Calcd for $C_9H_{11}N_2O_2F_3$: C, 45.77; H, 4.69; N, 11.86; F, 24.13. Found: C, 46.03; H, 4.86; N, 11.88; F, 23.91.

3-Trifluoromethyl-1-phenylpyrazole-4-carboxylic Acid 6c: mp 179-180 °C (hexane/$CHCl_3$); ir (KBr) 3675-2150, 1723 cm^{-1}; ^{1}H-nmr 8.43 (1H, s, H-5), 7.757.20 (6H, m, C_6H_5, OH). Anal. Calcd for $C_{11}H_7N_2O_2F_3$: C, 51.57; H, 2.75; N, 10.94; F, 22.25. Found: C, 51.43; H, 2.67; N, 10.84; F, 21.97.

1-(t-Butyl)-5-trifluoromethylpyrazole-4-carboxylic Acid 7b: mp 114-115 °C (hexane); ir (KBr) 3600-2170, 1718 cm^{-1}; ^{1}H-nmr 10.31 (1H, s, OH), 7.83 (1H, s, H-3), 1.69 (9H, s, $C(CH_3)_3$). Anal. Calcd for $C_9H_{11}N_2O_2F_3$: C, 45.77; H, 4.69; N, 11.86; F, 24.13. Found: C, 46.13; H, 4.78; N, 11.92; F, 23.81.

5-Trifluoromethyl-1-phenylpyrazole-4-carboxylic Acid 7c: mp 132-133 °C ($CHCl_3$); ir (KBr) 3530-2175, 1700 cm^{-1}; ^{1}H-nmr ($CD_3CN/CDCl_3$) 8.42 (1H, br s, OH), 8.09 (1H, s, H-3), 7.45 (5H, s, C_6H_5). Anal. Calcd for $C_{11}H_7N_2O_2F_3$: C, 51.57; H, 2.75; N, 10.94; F, 22.25. Found: C, 51.28; H, 2.68; N, 10.66; F, 22.14.

5-Trifluoromethyl-1-(p-nitrophenyl)pyrazole-4-carboxylic Acid 7d: mp 197-198 °C ($CHCl_3$); ir (KBr) 3600-2270, 1692 cm^{-1}; ^{1}H-nmr ($CD_3CN/CDCl_3$) 8.27 (2H, d, J=9, C_6H_4), 8.07 (1H, s, H-3), 7.57 (2H, d, J=9, C_6H_4), 7.33 (1H, br s, OH). Anal. Calcd for $C_{11}H_6N_3O_4F_3$: C, 43.87; H, 2.01; N, 13.95; F, 18.92. Found: C, 44.09; H, 1.94; N, 13.89; F, 18.89.

Reaction of β,β-Bis(trifluoroacetyl)vinyl i-Butyl Ether 1 with Benzaldehyde Methyl- and Phenylhydrazones; General Procedure: To a solution of **1** (0.59 g, 2 mmol) in MeCN (8 ml) was added benzaldehyde methyl- or phenylhydrazone (2 mmol). The whole mixture was stirred at room temperature for 0.5 h and the solvent was evaporated under reduced pressure to give **8** or **9**.

Benzaldehyde N-[β,β-Bis(trifluoroacetyl)vinyl]methylhydrazone 8: mp 120-121 °C (hexane/benzene); ir (KBr) 1733, 1668 cm^{-1}; ^{1}H-nmr 7.77 (2H, s, HC=), 7.37 (5H, s, C_6H_5), 3.57 (3H, s, CH_3). Anal. Calcd for $C_{14}H_{10}N_2O_2F_6$: C, 47.74; H, 2.86; N, 7.95; F, 32.36. Found: C, 47.83; H, 2.78; N, 7.68; F, 32.14.

Benzaldehyde N-[β,β-Bis(trifluoroacetyl)vinyl]phenylhydrazone 9: mp 142-143 °C (hexane/benzene); ir (KBr) 1753, 1660 cm^{-1}; ^{1}H-nmr 7.85 (1H, s, HC=), 7.626.96 (11H, m, $2C_6H_5$, HC=). Anal. Calcd for $C_{19}H_{12}N_2O_2F_6$: C, 55.08; H, 2.92; N, 6.76; F, 27.51. Found: C, 54.95; H, 2.73; N, 6.96; F, 27.41.

Conversion of Hydrazone 8 into Pyrazole 4a: To a solution of **8** (704 mg, 2 mmol) in $CHCl_3$ (6 ml) was added trifluoroacetic acid (1.5 ml, 19.5 mmol) containing a small amount of water. After stirring at room temperature for 3 h CH_2Cl_2 (100 ml) was added and the mixture was washed with ice-cold 10% aq. Na_2CO_3 (200 ml) and dried (Na_2SO_4). The solvent was evaporated to give the crude mixture of pyrazole **4a** and benzaldehyde. Fractional distillation under reduced pressure (100 °C/1 mmHg) afforded pure **4a** (374 mg, 76%).

Conversion of Hydrazone 9 into Pyrazole 4c: To a solution of **9** (829 mg, 2 mmol) in $CHCl_3$ (6 ml) was added trifluoroacetic acid (1.5 ml, 19.5 mmol) containing a small amount of water. After the reaction and work-up procedure as above, the crude mixture of pyrazole **4c** and benzaldehyde was obtained. Benzaldehyde was removed by distillation under reduced pressure (50 °C/1 mmHg) and the residue was submitted to chromatography to give pure **4c** (443 mg, 72%).

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Received, 26th December, 1991