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Trifluoroacetaldehyde hydrazones are condensed with glyoxals to give 4-hydroxy-3-trifluoromethylpyrazoles, the reaction offering a novel route to 4-hydroxypyrazoles carrying trifluoromethyl group. The 4-hydroxyl group was easily converted to its derivatives by the reaction with various electrophiles.

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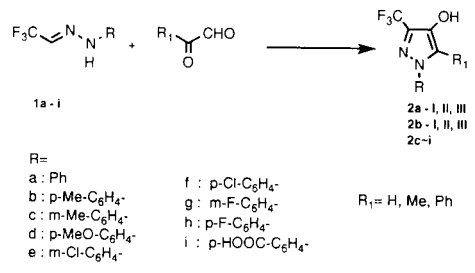
Many heterocyclic compounds bearing a trifluoromethyl (CF_3) group show some peculiar physiological activities, which have been applied for medicines and/or agrochemicals [1,2]. To develop the research on the physiological activities, the synthesis of various analogues becomes very important. An introduction of the reactive functional groups, such as an hydroxyl group, to the expected position of the target compounds must be effective to prepare designed analogues. For example, an introduction of a hydroxyl group into the 5-position of trifluoromethylpyrazoles can be achieved by the conventional condensation of the ethyl trifluoroacetoacetate with hydrazines [3]. In contrast, Begtrup and his coworker reported, recently, a new synthetic route to 4-hydroxypyrazoles, from aldehydehydrazones with α-ketoaldehydes (glyoxals) [4]. So we developed their method to the synthesis of a new series of 4-hydroxy-3-trifluoromethylpyrazoles using trifluoroacetaldehyde arylhydrazones, the 4-hydroxyl group of the products being subjected to substitution with various electrophiles to give many different 4-hydroxypyrazole derivatives. In this paper, we wish to describe the synthesis of these new compounds and to discuss the limitation of the reaction.

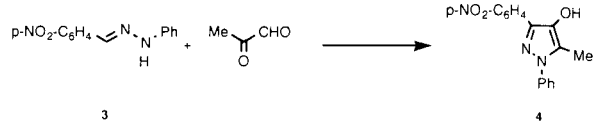
Trifluoroacetaldehyde phenylhydrazone (**1a**), prepared from trifluoroacetaldehyde ethylhemiacetal and phenylhydrazine [5], was reacted with glyoxal, methyl- and phenylglyoxals to give the corresponding 4-hydroxy-3-trifluoromethylpyrazoles **2a-I**, **II**, and **III** in moderate yields, respectively. Their structures were determined by spectral data and elemental analyses (Table I). In particular, the substituted position of the hydroxyl group was assigned on the basis of ^{13}C nmr analysis. The complete and off-resonance decoupling spectra of **2a-I** indicate the chemical shifts of pyrazole 3-, 4-, and 5-carbons are δ 131.7, 140.0, 116.0 ppm, respectively. The strongly deshielded 4-carbon and shielded 5-carbon support the hydroxyl group attached not to 5-carbon but to 4-carbon [6].

Scheme 1



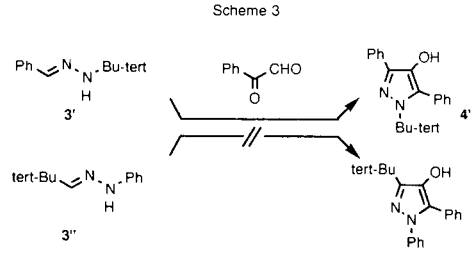
The trifluoroacetaldehyde arylhydrazones carrying electron releasing or slightly withdrawing groups on the phenyl ring condensed with glyoxals to give the corresponding pyrazoles, as summarized in Table I. In contrast the hydrazones having rather strong electron withdrawing groups, such as 4-NO_2-C_6H_4-, 2,4-$(NO_2)_2$-C_6H_3-, 4-CH_3-C_6H_4-SO_2-, CH_3CO-, and H_2NCS-, on the saturated nitrogen did not react and were recovered unchanged. However, *p*-nitrobenzaldehyde phenylhydrazone (**3**), bearing an electron withdrawing group on the hydrazone carbon, condensed with methylglyoxal to give the pyrazole **4** in 36% yield (Scheme 2).

Scheme 2



The steric requirement for this condensation was next investigated. The reactions of the hydrazones **3′** and **3′′**, the bulky *tert*-butyl group being attached to the saturated nitrogen or to the hydrazone carbon, respectively, with phenylglyoxal were carried out. While **3′′** did not afford the expected product, resulting in decomposition of **3′′**, **3′** gave the corresponding pyrazole **4′** in 39% yield (Scheme 3).

Scheme 3



Consequently, it should be noted that this condensation to 4-hydroxypyrazoles is retarded by the electron withdrawing groups, attached to the saturated nitrogen in particular, and the bulky groups on the hydrazone carbon.

Table I

Preparation of 4-Hydroxy-3-trifluoromethylpyrazoles **2**

Compound	R	R_1	Yield (%) [a]	Mp (°C) (Recrystallization Solvent)
2a-I	Ph	H	55	117.5-119.0 (hexane-chloroform)
2a-II	Ph	Me	51	150.5-152.5 (hexane-ethyl acetate)
2a-III	Ph	Ph	47	129.5-130.0 (hexane-ethyl acetate)
2b-I	*p*-Me-C_6H_4-	H	55	122.0-123.5 (hexane-ethyl acetate)
2b-II	*p*-Me-C_6H_4-	Me	52	132.0-133.0 (hexane-ethyl acetate)
2b-III	*p*-Me-C_6H_4-	Ph	33	140.5-142.5 (hexane-ethyl acetate)
2c	*m*-Me-C_6H_4-	Me	56	149.0-151.0 (hexane-ethyl acetate)
2d	*p*-MeO-C_6H_4-	Me	61	173.0-175.0 (hexane-ethyl acetate-ethanol)
2e	*m*-Cl-C_6H_4-	Me	50	127.0-129.0 (hexane-ethyl acetate)
2f	*p*-Cl-C_6H_4-	Me	31	155.0-157.0 (hexane-ethyl acetate)
2g	*m*-F-C_6H_4-	Me	39	156.0-157.0 (hexane-ethyl acetate)
2h	*p*-F-C_6H_4-	Me	41	172.5-173.5 (hexane-ethyl acetate)
2i	*p*-HOOC-C_6H_4-	Me	32	246.0-248.5 (hexane-ethyl acetate)

[a] Isolated yield.

Table II

Preparation of 4-Methoxy-, 4-Acetoxy, 4-Ethoxycarbonyloxy-, and Methoxycarbonylmethyloxy-5-methyl-3-trifluoromethylpyrazoles **5**, **6**, **7**, and **8**

Compounds	R	Yield (%) [a]	Mp (°C) (Recrystallization Solvent)
5a	Ph	86	52.0-53.5 (H_2O-ethanol)
5d	*p*-MeO-C_6H_4-	27	oil
5e	*m*-Cl-C_6H_4-	71	32.0-33.5 (ethanol)
5f	*p*-Cl-C_6H_4-	55	47.0-48.0 (H_2O-ethanol)
5h	*p*-F-C_6H_4-	79	oil
6a	Ph	65	62.0-62.5 (H_2O-ethanol)
6b	*p*-Me-C_6H_4-	60	79.0-81.3 (hexane)
6e	*m*-Cl-C_6H_4-	63	69.0-71.0 (hexane-ethyl acetate)
6f	*p*-Cl-C_6H_4-	39	72.0-73.0 (H_2O-ethanol)
6h	*p*-F-C_6H_4-	54	67.5-69.0 (hexane-ethyl acetate)
7a	Ph	65	oil
7b	*p*-Me-C_6H_4-	56	54.6-55.5 (hexane)
7e	*m*-Cl-C_6H_4-	40	64.0-66.0 (hexane)
7f	*p*-Cl-C_6H_4-	31	65.0-65.5 (H_2O-ethanol)
8a	Ph	71	oil
8h	*p*-F-C_6H_4-	52	oil

[a] Isolated yield.

Table III

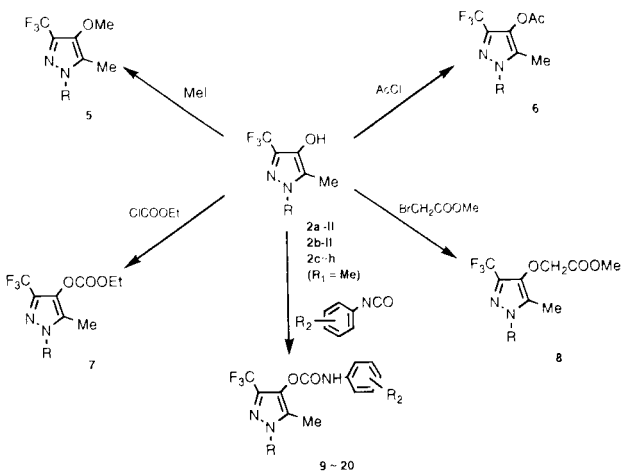
Preparation of 4-Arylcarbamoyloxy-5-methyl-3-trifluoromethylpyrazoles

Compounds	R	R_2	Yield (%) [a]	Mp (°C) (Recrystallization Solvent)
9	Ph	H	20	136.0-137.5 (hexane-ethanol)
10	*p*-Me-C_6H_4-	H	34	121.0-124.0 (hexane-ethyl acetate)
11	*m*-Cl-C_6H_4-	H	59	120.0-122.0 (hexane-ethyl acetate)
12	*p*-Cl-C_6H_4-	H	21	152.0-154.0 (hexane-ethanol)
13	*p*-F-C_6H_4-	H	34	140.0-142.0 (hexane-chloroform)
14	Ph	*p*-NO_2-	25	216.0-218.0 (hexane-ethyl acetate-ethanol)
15	*m*-Me-C_6H_4-	*p*-NO_2-	45	226.0-229.5 (ethyl acetate)
16	*m*-Me-C_6H_4-	*p*-Cl-	75	187.0-189.5 (ethyl acetate-chloroform)
17	*p*-F-C_6H_4-	*m*-Cl-	28	109.5-112.5 (hexane-chloroform)
18	Ph	*p*-CF_3-	32	188.0-191.0 (hexane-ethyl acetate)
19	Ph	*o*-Me-	88	116.0-118.0 (hexane-ethyl acetate)
20	*m*-Me-C_6H_4-	3,4-Cl_2-	84	146.5-148.5 (hexane-chloroform)

[a] Isolated yield.

Alkylation with iodomethane and methyl bromoacetate, acylation with acetyl chloride and ethyl chloroformate, and carbamoylation with aryl isocyanates of thus obtained pyrazoles **2** (R_1 = Me) were carried out. In any case, the reaction took place exclusively on the hydroxyl group to give the corresponding 4-hydroxypyrazole derivatives in good yields (Scheme 4 and Tables II and III).

Scheme 4



EXPERIMENTAL

The ir spectra were recorded on a JASCO A-100 spectrometer and samples were run as potassium bromide pellets or liquid films. The ^1H and ^{13}C nmr spectra were measured with JEOL JNM-PMX 60 and/or GX-270 spectrometers using tetramethylsilane as an internal standard, the chemical shifts being given in δ ppm downfield. Samples were prepared by dissolving in deuteriochloroform unless otherwise noted. The elemental analyses were measured with YANACO MT-3 equipment.

Trifluoroacetaldehyde arylhydrazones (**1**) were prepared by the reactions of trifluoroacetaldehyde ethylhemiacetal with the corresponding arylhydrazine, according to the methods reported in our previous paper [5].

Glyoxal hydrates were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate in the reaction solvent. The salt was filtered off and the filtrate was used for the next reaction.

Preparation of 4-Hydroxy-3-trifluoromethylpyrazoles **2**.

General Procedure.

A mixture of **1** (10 mmoles), glyoxal (2 equivalents), anhydrous magnesium sulfate (1.0 g), and a catalytic amount of acetic acid in butyl acetate was refluxed for 1-6 hours. After the solvent was removed, the residue was dissolved in aqueous sodium hydroxide solution (1 *M*), and the solution was washed with dichloromethane. The aqueous solution was acidified to *p*H 2 with concentrated hydrochloric acid, and extracted with dichloromethane. The extracts were washed with water and brine, dried over magnesium sulfate, and evaporated. The resulting solid **2** was purified by recrystallization. Yields, melting points, and recrystallization solvents were shown in Table I.

4-Hydroxy-1-phenyl-3-trifluoromethylpyrazole (**2a-I**).

The reaction for 4 hours produced **2a-I** (55%); ^1H nmr: δ 3.58 (br s, 1H), 7.18-7.56 (m, 6H); ^{13}C nmr: δ 116.0, 119.5, 124.5 (q), 127.7, 129.6, 131.7 (q), 139.4, 140.0; ^{13}C nmr (off-resonance decoupling): δ 116.0 (d), 119.5 (d), 124.5, 127.7, 129.6 (d), 131.7, 139.4, 140.0; ir: 3100 (OH), 1590 (C=C, C=N), 1110 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{10}H_7N_2F_3O$: C, 52.64; H, 3.09; N, 12.28. Found: C, 52.41; H, 2.81; N, 12.31.

4-Hydroxy-5-methyl-1-phenyl-3-trifluoromethylpyrazole (**2a-II**).

The reaction mixture was stirred at room temperature for 1 hour and refluxed for 1.5 hours to give **2a-II** (51%); ^1H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.30 (s, 3H), 7.45 (s, 5H), 8.14 (s, 1H); ^{13}C nmr: δ 9.5, 121.8, 124.8 (q), 128.3, 129.2, 132.0 (q), 137.0, 139.4; ir: 3040 (OH), 1578 (C=C, C=N), 1110 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{11}H_9N_2F_3O$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.65; H, 3.77; N, 11.59.

4-Hydroxy-1,5-diphenyl-3-trifluoromethylpyrazole (**2a-III**).

The reaction for 5 hours produced **2a-III** (47%); ^1H nmr: δ 4.66 (br s, 1H), 7.30 (m, 10H); ir: 3030 (OH), 1580, 1500 (C=C, C=N), 1118 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}N_2F_3O$: C, 63.16; H, 3.64; N, 9.21. Found: C, 63.08; H, 3.14; N, 9.26.

4-Hydroxy-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**2b-I**).

The reaction for 2 hours produced **2b-I** (55%); ^1H nmr: δ 2.39 (s, 3H), 4.00-4.50 (br s, 1H), 7.13-7.80 (m, 5H); ir: 3160 (OH), 1594, 1520 (C=C, C=N), 1106 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{11}H_9N_2F_3O$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.63; H, 3.95; N, 11.60.

4-Hydroxy-5-methyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**2b-II**).

The reaction for 2 hours produced **2b-II** (52%); ^1H nmr: δ 2.24 (s, 3H), 2.41 (s, 3H), 7.31 (s, 4H); ir: 3050 (OH), 1590, 1520 (C=C, C=N), 1126 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_2F_3O$: C, 56.25; H, 4.33; N, 10.93. Found: C, 56.42; H, 4.54; N, 10.70.

4-Hydroxy-5-phenyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**2b-III**).

The reaction for 3 hours produced **2b-III** (33%); ^1H nmr: δ 2.31 (s, 3H), 7.10-7.29 (m, 9H); ir: 3200 (OH), 1604, 1580, 1566, 1510 (C=C, C=N), 1120 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_2F_3O$: C, 64.15; H, 4.12; N, 8.80. Found: C, 64.00; H, 4.04; N, 8.61.

4-Hydroxy-5-methyl-1-(*m*-tolyl)-3-trifluoromethylpyrazole (**2c**).

The reaction for 3 hours produced **2c** (56%); ^1H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.21 (s, 3H), 2.38 (s, 3H), 7.22 (s, 4H), 7.81 (s, 1H); ir: 3070 (OH), 1610, 1586, 1496 (C=C, C=N), 1120 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_2F_3O$: C, 56.25; H, 4.33; N, 10.93. Found: C, 56.18; H, 4.16; N, 10.98.

4-Hydroxy-1-(*p*-methoxyphenyl)-5-methyl-3-trifluoromethylpyrazole (**2d**).

The reaction mixture was stirred at room temperature for 0.5 hours and refluxed for 4 hours to give **2d** (61%); ^1H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.20 (s, 3H), 3.84 (s, 3H), 6.88-7.40 (m, 4H), 7.97 (br s, 1H); ir: 3080 (OH), 1594, 1518 (C=C,

C=N), 1140 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_2F_3O_2$: C, 52.95; H, 4.07; N, 10.29. Found: C, 52.74; H, 4.09; N, 10.14.

1-(*m*-Chlorophenyl)-4-hydroxy-5-methyl-3-trifluoromethylpyrazole (**2e**).

The reaction mixture was stirred at room temperature for 1 hour and refluxed for 15 hours to give **2e** (50%); ^1H nmr: δ 2.20 (s, 3H), 6.51 (s, 1H), 7.25-7.51 (m, 4H); ir: 3090 (OH), 1580 (C=C, C=N), 1120 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2ClF_3O$: C, 47.76; H, 2.91; N, 10.13. Found: C, 47.82; H, 2.91; N, 10.19.

1-(*p*-Chlorophenyl)-4-hydroxy-5-methyl-3-trifluoromethylpyrazole (**2f**).

The reaction for 4 hours produced **2f** (31%); ^1H nmr: δ 2.23 (s, 3H), 7.37 (s, 4H); ir: 3110 (OH), 1596, 1498 (C=C, C=N), 1124 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2ClF_3O$: C, 47.76; H, 2.91; N, 10.13. Found: C, 47.52; H, 2.64; N, 10.10.

1-(*m*-Fluorophenyl)-4-hydroxy-5-methyl-3-trifluoromethylpyrazole (**2g**).

The reaction for 8 hours produced **2g** (39%); ^1H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.23 (s, 3H), 7.09-7.40 (m, 5H); ir: 3080 (OH), 1588 (C=C, C=N), 1138 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2F_4O$: C, 50.78; H, 3.10; N, 10.77. Found: C, 50.87; H, 2.90; N, 10.98.

1-(*p*-Fluorophenyl)-4-hydroxy-5-methyl-3-trifluoromethylpyrazole (**2h**).

The reaction mixture was stirred at room temperature for 1 hour and refluxed for 5 hours to give **2h** (41%); ^1H nmr: δ 2.21 (s, 3H), 6.98-7.50 (m, 5H); ir: 3130 (OH), 1600, 1520 (C=C, C=N), 1132 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2F_4O$: C, 50.78; H, 3.10; N, 10.77. Found: C, 50.75; H, 2.86; N, 10.67.

1-(*p*-Carboxyphenyl)-4-hydroxy-5-methyl-3-trifluoromethylpyrazole (**2i**).

The reaction for 6 hours produced **2i** (32%); ^1H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.33 (s, 3H), 5.70-6.70 (br 1H), 7.42-8.23 (m, 5H); ir: 3090 (OH), 1690 (C=O), 1600, 1578, 1510 (C=C, C=N) cm^{-1}.

Anal. Calcd. for $C_{12}H_9N_2F_3O_3$: C, 50.36; H, 3.17; N, 9.79. Found: C, 50.13; H, 3.02; N, 9.61.

Preparation of 4-Hydroxy-5-methyl-3-(*p*-nitrophenyl)-1-phenylpyrazole (**4**).

The similar procedure using **3** and methylglyoxal afforded dark red needle of **4** (36%), mp 193.2-195.1° (hexane-ethanol); ^1H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.30 (s, 3H), 7.40 (s, 5H), 8.20 (s, 4H); ir: 3120 (OH), 1690 (C=O), 1590, 1500 (C=C, C=N), 1320 (NO_2) cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.06; H, 4.45; N, 14.23. Found: C, 65.09; H, 4.52; N, 13.73.

Preparation of 1-*tert*-Butyl-3,5-diphenyl-4-hydroxypyrazole (**4'**).

The similar procedure using **3'** and methylglyoxal afforded a yellow powder of **4'** (39%), mp 126.0-128.0° (hexane-ethanol); ^1H nmr: δ 1.50 (s, 9H), 7.20-8.10 (m, 10H); ir: 3200 (OH), 3050, 2990 (CH), 1600, 1550 (C=C, C=N) cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.73; H, 6.49; N, 9.52.

Preparation of 4-Methoxy-5-methyl-3-trifluoromethylpyrazoles **5**.

General Procedure.

To a mixture of **2** (1 equivalent) and anhydrous potassium carbonate in acetone was added methyl iodide (4 equivalents) and the mixture was refluxed for 1-24 hours. After the salt was filtered off, the filtrate was evaporated to a residue which was extracted with dichloromethane. The extracts were washed with aqueous sodium hydroxide solution (1 *M*), dried over magnesium sulfate, and evaporated. The resulting product **5** was isolated by silica gel chromatography (eluent, hexane:ethyl acetate = 4:1) and purified by recrystallization, distillation, or separative glc. Yields, melting or boiling points, and recrystallization solvents are shown in Table II.

4-Methoxy-5-methyl-1-phenyl-3-trifluoromethylpyrazole (**5a**).

The reaction of **2a-II** produced **5a** (86%); ^1H nmr: δ 2.30 (s, 3H), 3.90 (s, 3H), 7.50 (s, 5H); ir: 1572, 1500 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_2F_3O$: C, 56.25; H, 4.33; N, 10.93. Found: C, 56.35; H, 4.24; N, 10.95.

4-Methoxy-5-methyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**5d**).

The reaction of **2d** produced **5d** (27%); ^1H nmr: δ 2.27 (s, 3H), 2.40 (s, 3H), 3.87 (s, 3H), 7.33 (s, 4H); ir: 1580, 1508 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}N_2F_3O$: C, 57.78; H, 4.85; N, 10.37. Found: C, 58.00; H, 4.85; N, 10.44.

1-(*m*-Chlorophenyl)-4-methoxy-5-methyl-3-trifluoromethylpyrazole (**5e**).

The reaction of **2e** produced **5e** (71%), ^1H nmr: δ 2.35 (s, 3H), 3.87 (s, 3H), 7.50 (s, 4H); ir: 1600 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_2ClF_3O$: C, 49.59; H, 3.47; N, 9.64. Found: C, 49.51; H, 3.29; N, 9.72.

1-(*p*-Chlorophenyl)-4-methoxy-5-methyl-3-trifluoromethylpyrazole (**5f**).

The reaction of **2f** produced **5f** (55%); ^1H nmr: δ 2.30 (s, 3H), 3.80 (s, 3H), 7.40 (s, 4H); ir: 1576, 1500 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_2ClF_3O$: C, 49.59; H, 3.47; N, 9.64. Found: C, 49.40; H, 3.20; N, 9.59.

1-(*p*-Fluorophenyl)-4-methoxy-5-methyl-3-trifluoromethylpyrazole (**5h**).

The reaction of **2h** produced **5h** (79%); ^1H nmr: δ 2.25 (s, 3H), 3.83 (s, 3H), 7.00-7.54 (m, 4H); ir: 1580, 1518 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_2F_4O$: C, 52.56; H, 3.68; N, 10.22. Found: C, 52.59; H, 3.44; N, 10.17.

Preparation of 4-Acetoxy-5-methyl-3-trifluoromethylpyrazoles **6**.

General Procedure.

To a diethyl ether solution of **2** (1 equivalent) and pyridine (4 equivalents) was added acetyl chloride (2.5 equivalents) and the mixture was refluxed for 1-29 hours. Excess ether was added to the reaction mixture. The mixture was washed with aqueous sodium hydroxide solution (1 *M*), water, and brine, dried over magnesium sulfate, and evaporated. The resulting solid was recrystal-

lized to give pure **6**. Yields, melting points, and recrystallization solvents were shown in Table II.

4-Acetoxy-5-methyl-1-phenyl-3-trifluoromethylpyrazole (**6a**).

The reaction of **2a-II** produced **6a** (65%); ^{1}H nmr: δ 2.20 (s, 3H), 2.33 (s, 3H), 7.50 (s, 5H); ir: 1752 (C=O), 1590 (C=C, C=N), 1142 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}N_2F_3O_2$: C, 54.93; H, 3.90; N, 9.86. Found: C, 55.14; H, 3.89; N, 9.74.

4-Acetoxy-5-methyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**6b**).

The reaction of **2b-II** produced **6b** (60%); ^{1}H nmr: δ 2.17 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 7.30 (s, 4H); ir: 1782 (C=O), 1198 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}N_2F_3O_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.31; H, 4.38; N, 9.57.

4-Acetoxy-1-(*m*-chlorophenyl)-5-methyl-3-trifluoromethylpyrazole (**6e**).

The reaction of **2e** produced **6e** (63%); ^{1}H nmr: δ 2.19 (s, 3H), 2.30 (s, 3H), 7.27-7.51 (m, 4H); ir: 1750 (C=O), 1590 (C=C, C=N), 1110 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_2ClF_3O_2$: C, 49.00; H, 3.16; N, 8.79. Found: C, 49.47; H, 3.00; N, 8.85.

4-Acetoxy-1-(*p*-chlorophenyl)-5-methyl-3-trifluoromethylpyrazole (**6f**).

The reaction of **2f** produced **6f** (39%); ^{1}H nmr: δ 2.17 (s, 3H), 2.33 (s, 3H), 7.40 (s, 4H); ir: 1754 (C=O), 1500 (C=C, C=N), 1142 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_2ClF_3O_2$: C, 49.00; H, 3.16; N, 8.79. Found: C, 48.81; H, 2.84; N, 8.42.

4-Acetoxy-1-(*p*-fluorophenyl)-5-methyl-3-trifluoromethylpyrazole (**6h**).

The reaction of **2h** produced **6h** (54%); ^{1}H nmr: δ 2.16 (s, 3H), 2.32 (s, 3H), 7.00-7.42 (m, 4H); ir: 1754 (C=O), 1592, 1510 (C=C, C=N), 1144 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_2F_4O_2$: C, 51.66; H, 3.34; N, 9.24. Found: C, 51.59; H, 3.25; N, 9.03.

Preparation of 4-Ethoxycarbonyloxy-5-methyl-3-trifluoromethylpyrazoles **7**.

General Procedure.

To a diethyl ether solution of **2** (1 equivalent) and triethylamine (3 equivalents) was added ethyl chloroformate (3 equivalents) and the mixture was stirred at room temperature for 2-14 hours. Excess ether was added to the reaction mixture and the mixture was washed with water, dried, and evaporated. The residual solid was recrystallized to give pure **7**. In the case of **7a**, purification was done by preparative glc. Yields, melting points, and recrystallization solvents were summarized in Table II.

4-Ethoxycarbonyloxy-5-methyl-1-phenyl-3-trifluoromethylpyrazole (**7a**).

The reaction of **2a-II** produced **7a** (65%); ^{1}H nmr: δ 1.39 (t, 3H), 2.27 (s, 3H), 4.35 (q, 2H), 7.51 (s, 5H); ir: 1770 (C=O), 1596, 1502 (C=C, C=N), 1126 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}N_2F_3O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C. 53.41; H, 4.10; N, 8.55.

4-Ethoxycarbonyloxy-5-methyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**7b**).

The reaction of **2b-II** produced **7b** (56%); ^{1}H nmr: δ 1.38 (t, 3H), 2.22 (s, 3H), 2.42 (s, 3H), 4.36 (q, 2H), 7.31 (s, 4H); ir: 1766 (C=O), 1126 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}N_2F_3O_3$: C, 54.88; H, 4.61; N, 8.53. Found: C, 54.94; H, 4.52; N, 8.60.

1-(*m*-Chlorophenyl)-4-ethoxycarbonyloxy-5-methyl-3-trifluoromethylpyrazole (**7e**).

The reaction of **2e** produced **7e** (40%); ^{1}H nmr: δ 1.43 (t, 3H), 2.30 (s, 3H), 4.38 (q, 2H), 7.41-7.51 (s, 4H); ir: 1768 (C=O), 1590, 1524 (C=C, C=N), 1136 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2ClF_3O_3$: C, 48.22; H, 3.47; N, 8.03. Found: C, 48.14; H, 3.44; N, 7.86.

1-(*p*-Chlorophenyl)-4-ethoxycarbonyloxy-5-methyl-3-trifluoromethylpyrazole (**7f**).

The reaction of **2f** produced **7f** (31%); ^{1}H nmr: δ 1.27 (t, 3H), 2.24 (s, 3H), 4.35 (q, 2H), 7.46 (s, 4H); ir: 1768 (C=O), 1590, 1524 (C=C, C=N), 1136 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2ClF_3O_3$: C, 48.22; H, 3.47; N, 8.03. Found: C, 47.77; H, 3.29; N, 7.71.

Preparation of 4-Methoxycarbonylmethyloxy-5-methyl-1-phenyl-3-trifluoromethylpyrazole (**8a**).

A mixture of **2a-II** (0.24 g, 1 mmole), anhydrous potassium carbonate (2.15 g), and ethyl bromoacetate (0.76 g, 5 mmoles) was refluxed for 6 hours. After the salt was filtered off, the filtrate was evaporated to leave a residue, which was extracted with dichloromethane. The extracts were washed with aqueous sodium hydroxide solution (1 *M*), water, and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (eluent, hexane:ethyl acetate = 1:1) to give pure yellow oil of **8a** (0.22 g, 71%); ^{1}H nmr: δ 2.37 (s, 3H), 3.80 (s, 3H), 4.75 (s, 2H), 7.47 (s, 5H); ir: 1758 (C=O), 1594 (C=C, C=N), 1124 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}N_2F_3O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.45; H, 4.21; N, 8.94.

1-(*p*-Fluorophenyl)-4-methoxycarbonylmethyloxy-5-methyl-3-trifluoromethylpyrazole (**8h**).

The similar procedure to the above afforded a yellow oil of **8h** (52%); ^{1}H nmr: δ 2.33 (s, 3H), 3.79 (s, 3H), 4.57 (s, 2H), 7.02-7.56 (s, 4H); ir: 1764 (C=O), 1590, 1516 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2F_4O_3$: C, 50.61; H, 3.64; N, 8.43. Found: C, 50.70; H, 3.68; N, 8.45.

Preparation of 4-Arylcarbamoyloxy-5-methyl-3-trifluoromethylpyrazoles.

General Procedure.

A solution of **2** (1 equivalent) and aryl isocyanate (5 equivalents) in toluene was refluxed for 3-51 hours in the presence of (for compounds **11**, **14-20**) or in the absence (for other compounds) of a catalytic amount of triethylamine. After the solvent was removed, the residue was washed with hexane and dissolved in diethyl ether or ethyl acetate. The organic layer was washed with aqueous sodium hydroxide solution (1 *M*), dried, and evaporated, the product being separated by silica gel chromatography and purified by recrystallization. Yields, melting points, and recrystallization solvents were collected in Table III.

5-Methyl-1-phenyl-4-phenylcarbamoyloxy-3-trifluoromethylpyrazole (**9**).

The reaction of **2a-II** with phenyl isocyanate produced **9** (20%); ^{1}H nmr: δ 2.30 (s, 3H), 7.10-7.50 (m, 11H); ir: 3370 (N-H), 1738 (C=O), 1590, 1500 (C=C, C=N), 1148 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_3F_3O_2$: C, 59.84; H, 3.91; N, 11.63. Found: C, 59.55; H, 3.53; N, 11.84.

5-Methyl-4-phenylcarbamoyloxy-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**10**).

The reaction of **2b-II** with phenyl isocyanate produced **10** (34%); ^{1}H nmr: δ 2.23 (s, 3H), 2.40 (s, 3H), 7.10-7.43 (m, 10H); ir: 3250 (N-H), 1750 (C=O), 1600 (C=C, C=N), 1138 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}N_3F_3O_2$: C, 60.80; H, 4.30; N, 11.19. Found: C, 60.95; H, 4.17; N, 11.33.

1-(*m*-Chlorophenyl)-5-methyl-4-phenylcarbamoyloxy-3-trifluoromethylpyrazole (**11**).

The reaction of **2e** with phenyl isocyanate gave **11** (59%); ^{1}H nmr: δ 2.32 (s, 3H), 7.07-7.52 (m, 10H); ir: 3250 (N-H), 1744 (C=O), 1590 (C=C, C=N), 1150 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_3ClF_3O_2$: C, 54.63; H, 3.31; N, 10.62. Found: C, 54.61; H, 3.22; N, 10.37.

1-(*p*-Chlorophenyl)-5-methyl-4-phenylcarbamoyloxy-3-trifluoromethylpyrazole (**12**).

The reaction of **2f** with phenyl isocyanate produced **12** (21%); ^{1}H nmr: δ 2.27 (s, 3H), 7.03-7.47 (m, 10H); ir: 3250 (N-H), 1750 (C=O), 1600, 1500 (C=C, C=N), 1144 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_3ClF_3O_2$: C, 54.63; H, 3.31; N, 10.62. Found: C, 54.58; H, 3.13; N, 10.48.

1-(*p*-Fluorophenyl)-5-methyl-4-phenylcarbamoyloxy-3-trifluoromethylpyrazole (**13**).

The reaction of **2h** with phenyl isocyanate produced **13** (34%); ^{1}H nmr: δ 2.24 (s, 3H), 7.02-7.56 (m, 10H); ir: 3250 (N-H), 1746 (C=O), 1602, 1510 (C=C, C=N), 1140 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_3F_4O_2$: C, 57.00; H, 3.45; N, 11.08. Found: C, 56.93; H, 3.22; N, 10.97.

5-Methyl-4-(*p*-nitrophenylcarbamoyloxy)-1-phenyl-3-trifluoromethylpyrazole (**14**).

The reaction of **2a-II** with *p*-nitrophenyl isocyanate gave **14** (25%); ^{1}H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.33 (s, 3H), 7.55-8.33 (m, 9H), 10.75 (s, 1H); ir: 3210 (N-H), 1758 (C=O), 1614, 1500 (C=C, C=N), 1558 (NO_2), 1138 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_4F_3O_4$: C, 53.21; H, 3.22; N, 13.79. Found: C, 53.09; H, 2.97; N, 13.96.

5-Methyl-4-(*p*-nitrophenylcarbamoyloxy)-1-(*m*-tolyl)-3-trifluoromethylpyrazole (**15**).

The reaction of **2c** with *p*-nitrophenyl isocyanate was carried out in 1,4-dioxane to give **15** (45%); ^{1}H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.28 (s, 3H), 2.43 (s, 3H), 7.30-8.26 (m, 8H), 10.49 (s, 1H); ir: 3250 (N-H), 1758 (C=O), 1612, 1596, 1508 (C=C, C=N), 1558 (NO_2), 1138 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}N_4F_3O_4$: C, 54.29; H, 3.60; N, 13.33. Found: C, 54.33; H, 3.40; N, 13.21.

4-(*p*-Chlorophenylcarbamoyloxy)-5-methyl-1-(*m*-tolyl)-3-trifluoromethylpyrazole (**16**).

The reaction of **2c** with *p*-chlorophenyl isocyanate was carried out in 1,4-dioxane to give **16** (75%); ^{1}H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.26 (s, 3H), 2.43 (s, 3H), 7.22-7.52 (m, 8H), 8.76 (s, 1H); ir: 3250 (N-H), 1746 (C=O), 1602, 1582, 1490 (C=C, C=N), 1134 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}N_3ClF_3O_2$: C, 55.69; H, 3.69; N, 10.25. Found: C, 55.75; H, 3.55; N, 10.05.

4-(*m*-Chlorophenylcarbamoyloxy)-1-(*p*-fluorophenyl)-5-methyl-3-trifluoromethylpyrazole (**17**).

The reaction of **2h** with *m*-chlorophenyl isocyanate produced **17** (28%); ^{1}H nmr: δ 2.25 (s, 3H), 7.06-7.45 (m, 8H), 7.58 (s, 1H); ir: 3260 (N-H), 1752 (C=O), 1598, 1510 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}N_3ClF_4O_2$: C, 52.25; H, 2.92; N, 10.16. Found: C, 52.10; H, 2.89; N, 10.13.

5-Methyl-1-phenyl-3-trifluoromethyl-4-(*p*-trifluoromethylphenylcarbamoyloxy)pyrazole (**18**).

The reaction of **2a-II** with *p*-trifluoromethylphenyl isocyanate produced **18** (32%); ^{1}H nmr (deuteriochloroform-dimethyl sulfoxide-d_6): δ 2.28 (s, 3H), 7.50-7.84 (m, 9H), 10.30 (s, 1H); ir: 3240 (N-H), 1756 (C=O), 1610, 1592 (C=C, C=N), 1144 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{19}H_{13}N_3F_6O_2$: C, 53.16; H, 3.05; N, 9.79. Found: C, 53.13; H, 2.89; N, 9.74.

5-Methyl-1-phenyl-4-(*o*-tolylcarbamoyloxy)-3-trifluoromethylpyrazole (**19**).

The reaction of **2a-II** with *o*-tolyl isocyanate produced **19** (88%); ^{1}H nmr: δ 2.30 (s, 3H), 2.36 (s, 3H), 6.87-7.94 (m, 10H), 10.30 (s, 1H); ir: 3260 (N-H), 1720 (C=O), 1592, 1582 (C=C, C=N), 1148 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}N_3F_3O_2$: C, 60.80; H, 4.30; N, 11.19. Found: C, 60.66; H, 4.29; N, 11.14.

4-(3,4-Dichlorophenylcarbamoyloxy)-5-methyl-1-(*m*-tolyl)-3-trifluoromethylpyrazole (**20**).

The reaction of **2c** with 3,4-dichlorophenyl isocyanate produced **20** (84%); ^{1}H nmr: δ 2.25 (s, 3H), 2.42 (s, 3H), 7.21-7.42 (m, 8H), 7.68 (s, 1H); ir: 3410 (N-H), 1728 (C=O), 1580, 1508 (C=C, C=N), 1130 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}N_3Cl_2F_3O_2$: C, 51.37; H, 3.18; N, 9.46. Found: C, 51.40; H, 3.01; N, 9.29.

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[6] The chemical shifts of 3, 4, and 5-carbon of 5-hydroxy-1-methyl-3-trifluoromethylpyrazole are reported to be δ 139.23, 84.78, and 153.54 ppm; see ref [3].