Convenient Synthesis of 4-Trifluoroacetylpyrazoles from Aldehyde *tert*-Butylhydrazones

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Several 1-(*tert*-butyl)-4-trifluoroacetylpyrazoles **3** were synthesized by the reaction of aldehyde *tert*-butylhydrazones **2** with 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**). The *tert*-butyl group could be readily removed by treatment of **3** with 90% sulfuric acid.

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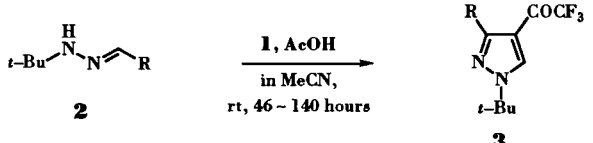
Many pyrazoles and their derivatives are known as pharmaceutically and medicinally active compounds which are applicable to agricultural chemicals and medicines [1]. Now, more convenient and effective synthetic methods to construct the pyrazole ring system is increasingly required. In the course of our investigation on the synthesis of 3-dialkylhydrazono-1,1,1-trifluoro-2-alkanones [2] and their interesting cyclization reactions accessible to several fluorine-containing heterocycles [3] we found a new convenient synthetic method to prepare 4-trifluoroacetylpyrazoles from aldehyde *tert*-butylhydrazones (**2**) and 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) [4].

$$EtOCH{=}CH_2 \xrightarrow[\text{in } CH_2Cl_2,\ rt,\ 3\ hours]{(CF_3CO)_2O,\ pyridine} EtOCH{=}CHCOCF_3$$

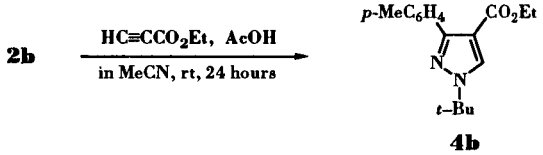
1

According to the usual approach [4] ethyl vinyl ether treated with trifluoroacetic anhydride in the presence of pyridine afforded **1** in high yields. Several aldehyde *tert*-butylhydrazones **2a-f** in acetonitrile was allowed to react with 1.2 equivalents of **1** thus obtained in the presence of 25 equivalents of acetic acid. The reaction proceeded at ambient temperatures and the corresponding 1-*tert*-butyl-4-trifluoroacetylpyrazoles **3a-f** were obtained in satisfactory yields (Table I). Quite similarly **2b** treated with ethyl propiolate in the presence of acetic acid afforded 1-*tert*-butyl-4-ethoxycarbonyl-3-(*p*-tolyl)pyrazole (**4b**) in 46% yield. The structures of **3a-f** and **4b** were established by ir,



2 **3**

a, R = Ph
b, R = p-MeC_6H_4
c, R = *p*-$MeOC_6H_4$
d, R = *p*-ClC_6H_4
e, R = *p*-$O_2NC_6H_4$
f, R = Et



4b

Table I

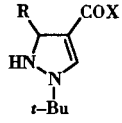
4-Trifluoroacetylpyrazoles **3a-f**, **7b** and 4-Ethoxycarbonylpyrazoles **4b**

Product	Time (h) [a]	Yield (%) [b]	Mp(°C) [c] or bp (°C)/Torr [d]	Molecular Formula or lit mp (°C)
3a	72	65	92	$C_{15}H_{15}F_3N_2O$ (296.3)
3b	48	61	$180/_5$	$C_{16}H_{17}F_3N_2O$ (310.3)
3c	76	66	64	$C_{16}H_{17}F_3N_2O_2$ (326.3)
3d	97	61	73	$C_{15}H_{14}ClF_3N_2O$ (330.7)
3e	140	34	75	$C_{15}H_{14}F_3N_3O_3$ (341.3)
3f	94	54	$135/_{10}$	$C_{11}H_{15}F_3N_2O$ (248.3)
4b	24	46	94	92 [3]
7b	8	92	137	$C_{12}H_9F_3N_2O$ (254.1)

[a] Reaction time. [b] Yield refers to pure isolated compounds. [c] Uncorrected, measured with a Mitamura Riken model 7-12 apparatus. [d] Oven temperature of Kugelrohr distillation.

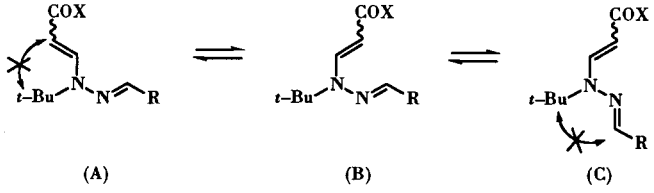
and ^1H and ^{13}C nmr spectroscopy and microanalysis. In the ^1H nmr spectra of **3a-f**, the pyrazole ring proton appears as a quartet at 7.83-8.10 ppm with long-range or through-space H-F coupling of 2.0 Hz. Similar long-range or through-space coupling with F nuclei are also observed for the pyrazole C5 in the ^{13}C nmr spectra.

Nucleophilic displacement of the ethoxy group of **1** by hydrazone **2** [5] or Michael type addition of **2** to ethyl propiolate to give acylvinyl hydrazone **5** or **6** followed by cyclization initiated by protonation on the azomethine nitrogen to result in formation of 2,3-dihydropyrazole **3'** or **4'** would be a possible pathway for the present reaction. Aromatization of the intermediate dihydropyrazole **3'** or **4'** to the product **3** or **4** should occur *via* air oxidation [6].



3', X = CF_3
4', X = OEt

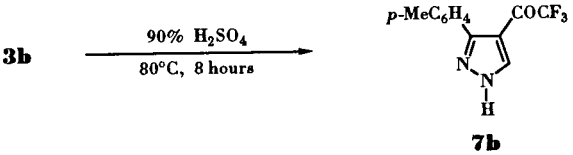
Unfortunately the reaction of aldehyde methylhydrazones instead of *tert*-butylhydrazones **2** and **1** did not give the corresponding 1-methyl-4-trifluoroacethylpyrazoles at all. Bulkiness of *tert*-butyl group should play an important role for the intermediate (**5** or **6**) to exist as a sterically more favored conformer (**B**), which is very convenient for the next cyclization to dihydropyrazole ring system. Removal of *tert*-butyl group of **3b** as a representative case



(A) (B) (C)

5, X = CF_3
6, X = OEt

was examined under several conditions. Among these heating **3b** in 90% sulfuric acid gave the best results and the corresponding *tert*-butyl free pyrazole **7b** was obtained in high yield.



7b

In conclusion, we present a very convenient as well as facile synthetic method to provide pyrazoles bearing a 4-trifluoroacetyl group, which can be converted to several fluoring-containing functionalities.

EXPERIMENTAL

All ^1H nmr spectra were recorded at 60 MHz on a JEOL PMX60SI spectrometer in deuteriochloroform solutions (unless otherwise noted) containing tetramethylsilane as an internal standard. The ^{13}C nmr spectra were measured in deuteriochloroform with a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. Infrared spectra was taken with a Hitachi model G3 spectrometer. 4-Ethoxy-1,1,1-trifluro-3-buten-2-one (**1**) was prepared according to a literature method [4].

1-*tert*-Butyl-4-trifluoroacetylpyrazoles **3a-f** and 1-*tert*-Butyl-4-ethoxycarbonylpyrazoles **4b**.

General Procedure.

To a well stirred mixture of **1** (1.08 g, 6 mmoles) or ethyl propiolate (491 mg, 5 mmoles) and acetic acid (4.3 ml, 75 mmoles) was added dropwise a solution of **2a-f** (5 mmoles) in acetonitrile (5 ml). After stirring for 48 hours at room temperature, dichloromethane (150 ml) was added and the whole mixture was washed with 1*N* aqueous sodium carbonate (200 ml). The mixture was dried (sodium sulfate) and the solvent was removed *in vacuo*. The residue was submitted to silica gel column chromatography using benzene/ethyl acetate (100:0-80:20) as eluent afforded pure **3a-f** or **4b**.

1-(*tert*-Butyl)-3-phenyl-4-trifluoroacetylpyrazole (**3a**).

This compound was obtained as pale yellow crystals (*n*-pentane); ir (potassium bromide): ν 1175-1200 (CF_3), 1700 (C=O) cm^{-1}; ^1H nmr: δ 1.64 (s, 9H, $C(CH_3)_3$), 7.20-7.77 (m, 5H, aryl), 8.00 (q, J = 2.0 Hz, 1H, CH).

Anal. Calcd. for $C_{15}H_{15}F_3N_2O$: C, 60.81; H, 5.10; N, 9.46. Found: C, 61.02; H, 5.18; N, 9.24.

1-(*tert*-Butyl)-3-(*p*-tolyl)-4-trifluoroacetylpyrazole (**3b**).

This compound was obtained as pale yellow oil; ir (potassium bromide): ν 1135-1200 (CF_3), 1700 (C=O) cm^{-1}; ^1H nmr: δ 1.66 (s, 9H, $C(CH_3)_3$), 2.43 (s, 3H, CH_3), 7.16, 7.60 (d, J = 8.0 Hz, 4H, aryl), 8.03 (q, J = 2.0 Hz, 1H, CH); ^{13}C nmr: δ 21.3, 29.3 (CH_3), 60.4 (C), 111.5 (pyrazole C4), 117.0 ($^1J_{CF}$ = 291.8 Hz, CF_3), 128.7, 129.2, 129.3 (aryl), 132.8 (J_{CF} = 4.9 Hz, pyrazole C5), 139.0 (aryl), 154.9 (pyrazole C3), 173.9 ($^2J_{CF}$ = 35.0 Hz, CO).

Anal. Calcd. for $C_{16}H_{17}F_3N_2O$: C, 61.93; H, 5.52; N, 9.03; F, 18.37. Found: C, 62.00; H, 5.58; N, 9.07; N, 18.33.

1-(*tert*-Butyl)-3-(*p*-methoxyphenyl)-4-trifluoroacetylpyrazole (**3c**).

This compound was obtained as pale yellow crystals (*n*-hexane/-chloroform); ir (potassium bromide): ν 1180-1200 (CF_3), 1695 (C=O) cm^{-1}; ^1H nmr: δ 1.63 (s, 9H, $C(CH_3)_3$), 3.75 (s, 3H, OCH_3), 6.78, 7.57 (d, J = 8.0 Hz, 4H, aryl), 7.93 (q, J = 2.0 Hz, 1H, CH).

Anal. Calcd. for $C_{16}H_{17}F_3N_2O_2$: C, 58.89; H, 5.25; N, 8.59. Found: C, 58.72; H, 5.15; N, 8.48.

1-(*tert*-Butyl)-3-(*p*-chlorophenyl)-4-trifluoroacetylpyrazole (**3d**).

This compound was obtained as pale yellow crystals (*n*-pentane); ir (potassium bromide): ν 1140, 1180, 1195 (CF_3), 1692 (C=O) cm^{-1}; ^1H nmr: δ 1.65 (s, 9H, $C(CH_3)_3$), 7.27, 7.64 (d, J = 8.2 Hz, 4H, aryl), 8.02 (q, J = 2.0 Hz, 1H, CH).

Anal. Calcd. for $C_{15}H_{14}ClF_3N_2O$: C, 54.47; H, 4.27; N, 8.47. Found: C, 54.45; H, 4.08; N, 8.57.

1-(*tert*-Butyl)-3-(*p*-nitrophenyl)-4-trifluoroacetylpyrazole (**3e**).

This compound was obtained as yellow crystals (*n*-hexane/chloroform); ir (potassium bromide): ν 1145, 1195 (CF_3), 1338, 1524 (NO_2), 1695 (C=O) cm^{-1}; ^1H nmr: δ 1.68 (s, 9H, $C(CH_3)_3$), 7.77-8.30, 8.10 (q and q, J = 8.5 Hz and J = 2.0 Hz, 5H, aryl and CH).

Anal. Calcd. for $C_{15}H_{14}F_3N_3O_3$: C, 52.79; H, 4.14; N, 12.31.

Found: C, 52.95; H, 4.06; N, 12.37.

1-(*tert*-Butyl)-3-ethyl-4-trifluoroacetylpyrazole (**3f**).

This compound was obtained as yellow oil; ir (potassium bromide): ν 1140, 1195 (CF_3), 1695 (C=O) cm^{-1}; ^1H nmr (tetrachloromethane): δ 1.22 (t, J = 7.2 Hz, 3H, CH_3), 1.58 (s, 9H, $C(CH_3)_3$), 2.86 (q, 2H, CH_2), 7.83 (q, J = 2.0 Hz, 1H, CH).

Anal. Calcd. for $C_{11}H_{15}F_3N_2O$: C, 53.22; H, 6.09; N, 11.28. Found: C, 52.92; H, 6.07; N, 11.20.

1-(*tert*-Butyl)-4-ethoxycarbonyl-3-(*p*-tolyl)pyrazole (**4b**).

This compound was obtained as colorless crystals; ir (potassium bromide): ν 1268, (C-O), 1705 (C=O) cm^{-1}; ^1H nmr: δ 1.25 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.60 (s, 9H, $C(CH_3)_3$), 2.33 (s, 3H, CH_3), 4.16 (q, 2H, CH_2), 7.06, 7.56 (d, J = 8.0 Hz), 7.91 (s, 1H, CH); ^{13}C nmr: δ 14.3, 21.2, 29.5 (CH_3), 59.2 (C), 59.8 (CH_2), 110.7 (pyrazole C4), 128.4, 129.2, 130.2 (aryl), 131.4 (pyrazole C5), 137.8 (aryl), 152.3 (pyrazole C3), 163.4 (CO).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.26; H, 7.88; N, 9.85.

3-(*p*-Tolyl)-4-trifluoroacetylpyrazole (**7b**).

A mixture of **3b** (310 mg, 1 mmole) and 90% sulfuric acid (5 ml) was stirred for 8 hours at 80°. The reaction mixture was poured into 2*N* aqueous sodium carbonate (100 ml) and extracted with dichloromethane (50 ml x 2). The organic layer was dried (sodium sulfate) and the solvent was removed *in vacuo* gave pale yellow crystals, which was recrystallized from tetrachloromethane to yield 233 mg (92%) of **7b** as colorless crystals; ir (potassium bromide): ν 1135-1200 (CF_3), 1700 (C=O) cm^{-1}; ^1H nmr: δ 2.43 (s, 3H, CH_3), 7.16, 7.47 (d, J = 8.0 Hz, 4H, aryl), 7.90-8.10 (br, 2H, CH and NH).

Anal. Cacld. for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.92; H, 3.53; N, 11.11.

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[6] When the reaction of **1** and **2b** was carried out under nitrogen atmosphere, the signals (1.23 (s), 4.80 (br), 7.73 (q) ppm) attributable to *tert*-butyl and methine protons of intermediate 2,3-dihydropyrazole **3'** (R = *p*-MeC_6H_4) were observed together with those of **3b** in the ^1H nmr spectra of the crude product obtained after the usual workup. During process of purification or even by standing for a few hours under atmospheric conditions this intermediate completely aromatized to **3b**.