Synthesis and ^{13}C NMR of (Trifluoromethyl)hydroxypyrazoles

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Reaction of ethyl 4,4,4-trifluoroacetoacetate with methylhydrazine produced not only the previously reported 5-hydroxy-3-(trifluoromethyl)pyrazole **1** but also its unknown isomer the 3-hydroxy-5-(trifluoromethyl)pyrazole **4**. The structure assignments are established based on ^{13}C nmr spectra. Compound **1** was converted to 5-chloro-3-(trifluoromethyl)pyrazolecarboxylic acid **3** in two steps.

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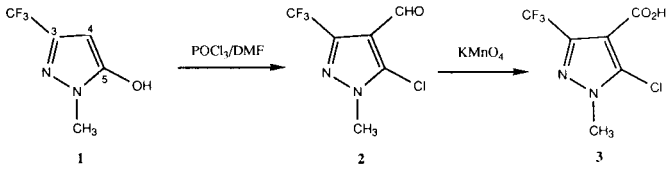
In a previous communication [1] we described the synthesis of a series of 2-halo-4-(trifluoromethyl)-5-thiazolecarboxylates which possess herbicide antidote activity for α-chloroacetanilide herbicides. In an effort to determine whether other trifluoromethylated haloheterocycles also possess similar herbicide antidote activity, we decided to synthesize the hitherto unknown 5-chloro-1-methyl-3-(trifluoromethyl)-4-pyrazolecarboxylic acid (**3**).

It was envisioned that **3** might be prepared from the known 5-hydroxypyrazole **1** *via* the 5-chloro-4-carboxaldehyde **2** (Scheme 1). Compound **1** was reported as the only isolated product (mp 174-175.5°) from the reaction of ethyl 4,4,4-trifluoroacetoacetate (ETFAA) with methylhydazine [2]. However, there are no other physical data besides ir to confirm that the product was indeed **1** instead of its isomer, the 3-hydroxypyrazole **4**.

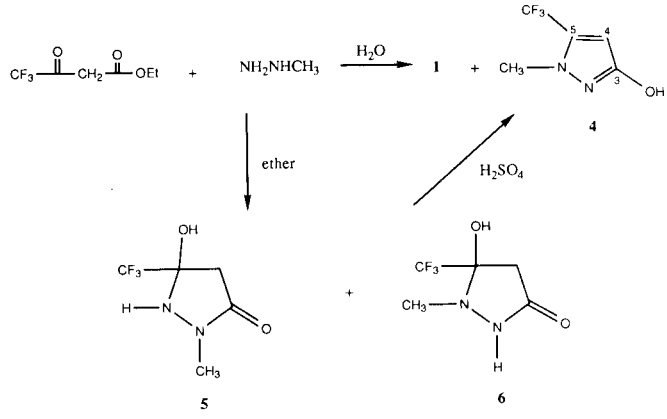
Scheme 1



1 2 3

In contrast to the literature results, we found the reaction of ETFAA with aqueous methylhydrazine produced two products with the respective melting points of 173-175° and 129.5-131.5° in a ratio of 4:1 (Scheme 2). The higher melting solid was the major product. The combustion analyses and the ^1H and ^{19}F nmr spectra of both products are consistent with either the structure **1** or **4**. The higher melting material exhibits a ring ^1H nmr (DMSO-d_6) signal at δ 5.73 and a methyl ^1H signal at δ 3.60. It also has a ^{19}F signal at δ −62.03. The lower melting material exhibits the ring ^1H signal at δ 5.93, the methyl ^1H signal at δ 3.77 and the trifluoromethyl ^{19}F signal at δ −59.90. These minor differences in the ^1H and ^{19}F chemical shifts are insufficient for a definitive structure assignment.

Scheme 2



However, upon examining the ^{13}C nmr spectra (Table 1) one can clearly assign the structure **1** to the higher melting material and the structure **4** to the lower melting solid. The proton decoupled ^{13}C nmr of the higher melting solid shows the methyl carbon as a singlet at δ 33.89 but the methyl carbon of the lower melting solid exhibits as a quartet at δ 37.38 with a coupling constant $^4J_{CF} = 1.4$ Hz. Furthermore, the proton coupled ^{13}C nmr of the higher melting material shows that C-5 (δ 153.54) is coupled not only with the ring proton but also with the methyl protons. On the other hand, C-5 (δ 131.15) of the lower melting material is coupled with both the ring and the methyl protons as well as the trifluoromethyl fluorine. Based on the above

Table 1. ^{13}C NMR Spetra[a] of Hydroxypyrazoles 1 And 4

Compound No.	C-3	C-4	C-5	CF_3	CH_3
	Chemical Shifts[b] And Coupling Constants[c].				
1	139.03 (dq)	84.78 (qd)	153.54 (qd)	122.00 (q)	33.89 (q)
	$^2J_{CH}$ = 3.7, $^2J_{CF}$ =37.1	$^1J_{CH}$ = 180.9, $^3J_{CF}$ = 2.2	$^2J_{CH}$ = 4.8, $^3J_{CH}$ = 2.2	$^1J_{CF}$ = 268.1	$^1J_{CH}$ = 140.46
4	160.28 (d)	92.81 (qd)	131.15 (dqq)	120.17 (q)	37.38 (qq)
	$^2J_{CH}$ = 1.2	$^1J_{CH}$ = 180.96, $^3J_{CF}$ = 2.6	$^2J_{CH}$ = 5.2, $^3J_{CH}$ = 2.2, $^2J_{CF}$ = 38.2	$^1J_{CF}$ = 268.0	$^1J_{CH}$ = 141.2, $^4J_{CF}$ = 1.4

[a] in DMSO-d_6; proton coupled spectra. [b] δ in ppm; multiplicity in parenthesis; d: doublet, q: quartet, dq: doublet of quartet, qd: quartet of doublet, qq: quartet of quartet, dqq: doublet of quartet of quartet. [c] *J* in Hz.

data the structures of **1** and **4** were established without doubt for the higher and the lower melting solids, respectively.

We also found that if the reaction of ETFAA with anhydrous methylhydrazine was carried out in ether the initial products were a 4:1 mixture of **5** and **6** (Scheme 2) as evidenced by the ^{19}F nmr absorptions at δ −83.00 and −81.56, respectively, which are substantially higher field signals than those of **1** and **4**. The major isomer **5** can be easily separated from the minor isomer by recrystallization from chloroform. The mixture of **5** and **6** can be dehydrated readily with sulfuric acid to give a mixture of **1** and **4**, which are easily separable due to higher solubility of **1** in sodium bicarbonate. In this manner, **4** was obtained in better yields (25%) [3].

Reaction of **1** with phosphorus oxychloride and dimethylformamide gave the aldehyde **2** in 40% yield. Oxidation of **2** with potassium permanganate provided the desired acid **3** in 63% yield. Compound **3** did not exhibit substantial herbicide antidote activity.

EXPERIMENTAL

Melting points were taken in open capillaries in a Mel-Temp apparatus and are uncorrected. The ^1H and the ^{19}F nmr spectra were recorded on a Varian EM-360L (60 MHz) spectrometer. The ^{13}C nmr spectra were measured at 25.05 MHz with a JEOL FX-100 spectrometer. The ^1H and ^{13}C nmr spectra are expressed in part per million (ppm) downfield from tetramethylsilane. The ^{19}F nmr spectra are expressed in ppm upfield from fluorotrichloromethane. Infrared spectra were recorded on a Perkin Elmer 727b spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

Reaction of Ethyl 4,4,4-trifluoroacetoacetate (ETFAA) with Aqueous Methylhydrazine; Isolation of 1-Methyl-5-hydroxy-3-(trifluoromethyl)pyrazole (**1**) and 1-Methyl-3-hydroxy-5-(trifluoromethyl)pyrazole (**4**).

To a mixture of 55.2 g (0.30 mole) of ETFAA and 50 ml of water was added 27.64 g (0.60 mole) of methylhydrazine at once, causing a violent reaction. After the reaction subsided, the mixture was held at reflux for 2 hours and cooled to room temperature overnight. Long needle crystals formed and were filtered to give 4.2 g (8%) of **4**, mp 129.5-131.5°; ir (nujol): 3550, 3400-2600, 1550 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.16 (s, broad, 1 H, OH), 6.03 (s, 1 H, C=CH), 3.73 (s, 3 H, NCH_3).

Anal. Calcd. for $C_5H_5F_3N_2O$: C, 36.15; H, 3.03; N, 16.87. Found: C, 36.17; H, 3.07; N, 16.91.

The filtrate was acidified to *p*H 1 and the precipitate was collected and stirred with chloroform. The chloroform insoluble material was filtered to give 24.2 g (49%) of **1** as white prisms, mp 172-175° (lit [2] mp 174-175.5°); ir (nujol): 3500-2300, 1550 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.73 (s, 1 H, C=CH), 3.60 (s, 3 H, NCH_3). The OH signal is too broad to be located.

Anal. Calcd. for $C_5H_5F_3N_2O$: C, 36.15; H, 3.03; N, 16.87. Found: C, 36.14; H, 3.04; N, 16.87.

Reaction of ETFAA with Anhydrous Methylhydrazine in Ether, Isolation of 1-Methyl-3-hydroxy-3-(trifluoromethyl)-2,3,4,5-tetrahydropyrazol-5-one (**5**).

To a cold (0°) solution of 1755 g (9.54 moles) of ETFAA in 3 ℓ of ether was added dropwise 439 g (9.53 moles) of methylhydrazine. After complete addition of methylhydrazine, the reaction mixture was allowed to rise to room temperature and was stirred overnight. Analysis of an aliquot of the reaction mixture by ^{19}F nmr (DMSO-d_6) showed that the mixture contained a 4:1 mixture of **5** and **6** with the ^{19}F signals at δ −83.00 and −81.57, respectively. These signals disappeared upon treatment with sulfuric acid and two new signals at δ −63.03 and −59.90 corresponding to **1** and **4**, respectively, appeared. After removal of the majority of ether by distillation, 5 ℓ of chloroform was added to the residue and the mixture was held at reflux for 0.5 hour then was allowed to cool overnight. The insoluble material was filtered to give 1196 g (68%) of **5** as prisms (mp 101-105°). A portion (7.79 g) of this material was recrystallized from chloroform-acetone to give 6.16 g of an analytical sample, mp 104.5-107.5°; ^1H nmr (DMSO-d_6): δ 7.43 (s, 1 H), 6.20 (s, 1 H), 2.90 (s, 3 H, NCH_3), 2.70 (s, 2 H, CH_2): ^{19}F nmr (DMSO-d_6): δ −83.00.

Anal. Calcd. for $C_5H_7F_3N_2O_2$: C, 32.63; H, 3.82; N, 15.18. Found: C, 32.65; H, 3.84; N, 15.19.

The original chloroform filtrate was stirred with 4 ℓ of 4% sodium bicarbonate. The organic layer was separated and concentrated *in vacuo*. The residue was recrystallized from methylcyclohexane to give 220 g (14%) of **4**.

Improved Synthesis of **4**.

To an ice-water cooled solution of 6.16 kg (33.5 moles) of ETFAA in 6 kg of ether was added 1.54 kg (33.5 moles) of methylhydrazine at such a rate that the reaction mixture was maintained at 24-26°. After one additional hour of stirring the reaction mixture was concentrated to remove most of the ether. To the residue was added 12 ℓ of chloroform followed by 150 ml of sulfuric acid. The reaction mixture was stirred overnight and the resulting slurry was washed successively with 3 ℓ of water once, 3 ℓ of saturated sodium bicarbonate five times and then 3 ℓ of water twice to remove the isomer **1**. The sodium bicarbonate insoluble solid was extracted into chloroform (2 x 4 ℓ). The chloroform extract was concentrated *in vacuo* to give 1.4 kg (25%) of **4**.

5-Chloro-1-methyl-3-(trifluoromethyl)-4-pyrazolecarboxaldehyde (**2**).

The procedure of Porai-Koshits *et al.* [4] was adopted. To a well stirred cold (0°) solution of 8.77 g (0.12 mole) of DMF was added 39.76 g (0.26 mole) of phosphorus oxychloride. The resulting slurry mixture was warmed to room temperature. To the above mixture was added 19.96 g (0.12 mole) of **1** and the mixture was heated at 110° for 16 hours, cooled, and poured into ice water. The aqueous mixture was neutralized to *p*H 4-6 and the precipitate was filtered to give 12.3 g of a brown solid which was recrystallized from hexane to give 10.1 g (40%) of **2** as yellow needles, mp 39.5-41° ir (chloroform): 2760, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.0 (s, 1 H, CHO), 3.93 (s, 3 H, NCH_3).

Anal. Calcd. for $C_6H_4ClF_3N_2O$: C, 33.90; H, 1.90; N, 13.18. Found: C, 33.93; H, 1.92; N, 13.19.

5-Chloro-1-methyl-3-(trifluoromethyl)-4-pyrazolecarboxylic Acid (**3**).

A mixture of 8.48 g (0.04 mole) of **2**, 6.32 g (0.04 mole) of potas-

sium permanganate, 0.2 g of potassium hydroxide and 75 ml of water was stirred at 60° for 1 hour and filtered. The filtrate was acidified to give 7.0 g of solid which was boiled with chloroform. The hot chloroform solution was filtered. The filtrate was concentrated and the residue was recrystallized from ethanol-water to give 5.76 g (63%) of **3**, mp 198-201°; ir (nujol): 3300-2300, 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.93 (s, NCH_3), the OH signal was too broad to be located.

Anal. Calcd. for $C_6H_4ClF_3N_2O_2$: C, 31.53; H, 1.76; N, 12.26; Cl, 15.51. Found: C, 31.21; H, 1.77; N, 12.09; Cl, 15.37.

REFERENCES AND NOTES

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[4] B. A. Porai-Koshits, I. Y. Kvitko, E. A. Shutkova, *Khim. Farm. Zh.*, **4**, 19 (1970); *Chem. Abstr.*, **73**, 3844 (1970).