Synthesis of 1-Aryl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic Acids and Esters

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Ethyl 1-aryl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylates **2** were prepared by the condensation of arylhydrazines with ethyl 3-ethoxy-2-(trifluoroacetyl)-2-propenoate (**1a**) at low temperature. The corresponding acids were also synthesized. X-ray diffraction analysis of an amide derivative **4** verified the position of the trifluoromethyl group on the pyrazole ring.

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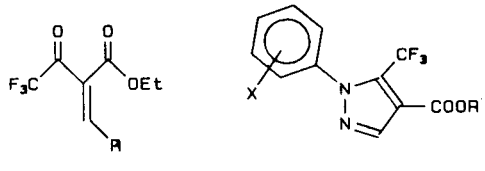
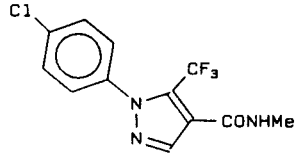
Reuben Jones [1] reported the synthesis of ethyl 3-ethoxy-2-(trifluoroacetyl)-2-propenoate (**1a**) by the condensation of ethyl 4,4,4-trifluoroacetate with triethyl orthoformate. We were interested in **1a** as a potential precursor for the preparation of pyrazoles containing trifluoromethyl functionality. Initial reaction of arylhydrazines with **1a** at the enol ether function would lead to ethyl 1-aryl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylates **2**. Initial reaction at the activated keto carbonyl would lead to the corresponding 3-trifluoromethyl isomers.



1a R = OEt
1b R = NMe_2

2 R = Et
3 R = H



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Condensation of phenylhydrazine with **1a** under ordinary conditions utilized in pyrazole synthesis was exothermic and led to complex mixtures. An attempt was made to synthesize ethyl 3-dimethylamino-2-(trifluoroacetyl)-2-propenoate (**1b**) as an alternative precursor to the desired pyrazoles. Reaction of ethyl 4,4,4-trifluoroacetoacetate with *N,N*-dimethylformamide dimethyl acetal resulted in the formation of ethyl 3-dimethylamino-2-propenoate [2] in 75% yield. Apparently, the methanol formed reacted with **1b** to yield the unexpected product and methyl trifluoroacetate, although the latter was not positively identified as a product of the reaction.

Finally, it was found that the slow addition of **1a** to a solution of phenylhydrazine in ethanol, keeping the temperature below −10°, led to the formation of the desired ethyl 1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**2a**) (Table I) in 78% yield. The trifluoromethyl group was assigned to the 5-position based on the ^{1}H nmr spectrum of **2a**. Tensmeyer and Ainsworth [3] reported that phenyl protons in phenyl substituted pyrazoles showed essentially a singlet, if an adjacent substituent was present. In the absence of *ortho* substituents on the pyrazole ring, the phenyl protons always appeared as a multiplet. The nmr spectrum of **2a** showed a singlet at δ 7.46 (60 MHz, deuteriochloroform). Similarly prepared were the related esters **2b-e** (Table I).

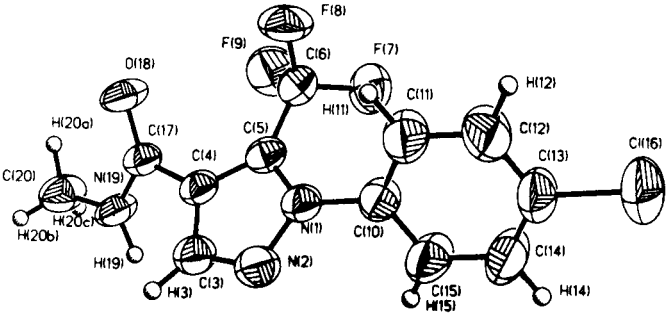

Figure 1. ORTEP plot of **4** with the numbering scheme used in the crystallographic study.

Table I

Ethyl 1-Aryl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylates

Compound	X	Yield, %	Mp °C	Calcd. % (Found) C	H	N
2a	H	78	−−[a]	54.93	3.90	9.86
				(54.66	3.97	9.97)
2b	3-Cl	64	66-68	49.00	3.16	8.79
				(49.21	3.32	8.95)
2c	4-Cl	65	51-53	49.00	3.16	8.79
				(48.87	3.19	8.70)
2d	3-CF_3	71	39-41	47.74	2.86	7.95
				(47.89	2.88	7.83)
2e	4-OMe	73	49-51	53.51	4.17	8.91
				(53.38	4.04	8.72)

[a] Bp 120-125°/0.05-.075 mm.

Table II

1-Aryl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic Acids

Compound	X	Yield, %	Mp °C	Calcd. % (Found) C	H	N
3a	H	67	129-131	51.57	2.75	10.93
				(51.41	2.53	10.86)
3b	3-Cl	61	148-150	45.46	2.08	9.64
				(45.73	1.88	9.82)
3c	4-Cl	67	136-138	45.46	2.08	9.64
				(45.19	2.43	9.85)
3d	3-CF_3	66	157-159	44.46	1.87	8.64
				(44.73	1.64	8.72)
3e	4-OMe	66	164-165	50.36	3.17	9.79
				(50.14	2.92	9.73)

The esters were hydrolyzed to the corresponding carboxylic acids **3a-e** in 60-70% yield (Table II). The *N*-methylcarboxamide **4** of **3c** was prepared and subjected to X-ray diffraction analysis. The ORTEP plot is shown in Figure 1.

Table III

Atom Coordinates (x 10^4) and Temperature Factor (Å^2 x 10^3)

atom	*x*	*y*	*z*	*U*[a]
Cl(16)	1330(5)	4497(1)	2907(2)	121(1)
N(1)	4483(8)	6323(1)	2250(3)	53(1)
N(2)	6747(9)	6508(1)	3280(4)	64(1)
C(3)	6750(11)	6921(1)	2912(4)	60(2)
C(4)	4471(10)	7007(1)	1653(4)	49(1)
C(5)	3027(9)	6618(1)	1238(4)	48(1)
C(6)	485(10)	6512(1)	−18(4)	58(2)
F(7)	−1403(6)	6200(1)	205(3)	81(1)
F(8)	1517(7)	6363(1)	−1076(3)	86(1)
F(9)	−1310(7)	6844(1)	−511(3)	88(1)
C(10)	3732(11)	5877(1)	2396(4)	56(2)
C(11)	3988(15)	5576(1)	1425(6)	86(2)
C(12)	3268(15)	5150(2)	1595(6)	91(3)
C(13)	2337(13)	5029(1)	2728(5)	76(2)
C(14)	2075(18)	5331(2)	3695(6)	100(3)
C(15)	2789(15)	5757(2)	3532(5)	85(3)
C(17)	3857(10)	7434(1)	919(4)	50(1)
O(18)	3416(8)	7471(1)	−349(3)	67(1)
N(19)	3817(9)	7768(1)	1764(3)	61(1)
C(20)	3445(14)	8207(1)	1242(5)	74(2)

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalised U_{ij} tensor.

Compound **4** was crystallized from toluene in the monoclinic space group $P2_1/c$, with four molecules in a unit cell having the dimensions a = 4.477(1) Å, b = 30.915(6) Å, c = 9.908(1) Å, and β = 106.660°. The calculated density was 1.535 g/cm^3. Intensities of 1917 unique reflections with 2θ less than 116.0 were measured on a 4-angle diffractometer using monochromatic copper radiation. Positions of the atoms were obtained by interpretation of an *E* map phased by the direct methods routine SOLV of the SHELXTL program. The structure was refined by the least-squares method with anisotropic temperature factors for all atoms and with hydrogen atoms at calculated positions. The final R-factor was 0.0670 for 1382 observed reflections. Table III shows unit cell atomic coordinates.

EXPERIMENTAL [4]

Reaction of Ethyl 4,4,4-Trifluoroacetoacetate with *N,N*-Dimethylformamide Dimethyl Acetal

A solution containing 25.0 g (0.136 mole) of ethyl 4,4,4-trifluoroacetoacetate, 24.2 g (0.20 mole) of *N,N*-dimethylformamide dimethyl acetal, and 200 mg of *p*-toluenesulfonic acid was heated on the steam bath in an open flask for 1 hour. The mixture was distilled to yield 14.6 g (75%) of ethyl 3-dimethylamino-2-propenoate, bp 100-101°/3 mm; lit [2] bp 84-85°/1.4 mm; ms: 143 (M^+).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.43; H, 9.32; N, 9.72.

General Synthesis of Ethyl 1-Aryl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylates **2a-e**.

To a cold solution or suspension (−15°) containing 0.06 mole of the appropriate arylhydrazine hydrochloride and 0.06 mole of triethylamine in 100 ml of ethanol was added dropwise 0.06 mole of **1a** [1] during a 45 minute period. The temperature was not allowed to exceed −10°C during the addition. The mixture was stirred and allowed to reach ambient temperature during 1 hour. The solvent was removed *in vacuo*. The crude mixture was shaken with equal parts of diethyl ether and water. The organic layer was washed successively with *1N* hydrochloric acid, water, and saturated sodium bicarbonate and brine solutions and dried with sodium sulfate. The solvent was removed *in vacuo*, and the product was either distilled (**1a**) or crystallized from hexane (**1b-e**) (Table I).

General Synthesis of 1-Aryl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic Acids **3a-e**.

A solution containing 0.06 mole of the appropriate **2** and 0.09 mole of potassium hydroxide in 150 ml of ethanol was stirred and refluxed for 2 hours. The solution was diluted with 600 ml of water and extracted with 250 ml of diethyl ether. The aqueous layer was acidified with concentrated hydrochloric acid. The solid was collected and crystallized from toluene (Table II).

1-(4-Chlorophenyl)-*N*-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide (**4**).

To a solution containing 21.8 g (0.075 mole) of **3c** in 150 ml of dimethylformamide was added portionwise 14.0 g (0.086 mole) of 1,1'-carbonyldiimidazole. The mixture was stirred for 20 minutes. Forty percent aqueous methylamine solution (50 ml, 0.35 mole) was added, and the solution was stirred at ambient temperature for 3 hours. The mixture was slowly poured into 1000 ml of ice-water with rapid stirring. The solid was collected and crystallized from toluene to yield 20.25 g (89%) of product, mp 156-157°.

Anal. Calcd. for $C_{12}H_9ClF_3N_3O$: C, 47.46; H, 2.99; N, 13.84. Found: C, 47.57; H, 3.05; N, 13.85.

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REFERENCES AND NOTES

[1] R. G. Jones, *J. Am. Chem. Soc.*, **73**, 3684 (1951).

[2] P. L. De Benneville and J. H. Macartney, *ibid.*, **72**, 3725 (1950).

[3] L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

[4] Melting points were determined on a Mel-Temp apparatus and are uncorrected. A portion of the experimental work was published previously: J. R. Beck and M. P. Lynch, British Patent Application, 2,149,402A (1985).