Synthesis of 1-(1,1-Dimethylethyl)-1*H*-pyrazole-4-carboxylate Ester Derivatives

James R. Beck* and Michael P. Lynch

Lilly Research Laboratories, Division of Eli Lilly and Company,
Greenfield, Indiana 46140

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Attempts to prepare ethyl 5-cyano-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylate (**7**) by the reaction of the corresponding 5-chloro derivative **1b** with cyanide ion were unsuccessful. The chloro ester was synthesized from the corresponding amino ester **1a** utilizing nonaqueous diazotization with nitrosyl chloride. An alternate process was developed which allowed the preparation of **7** from the corresponding 5-methyl ester **3** in four steps. The structure of the *N*-methylamide **8** synthesized from **7** was confirmed by X-ray diffraction analysis.

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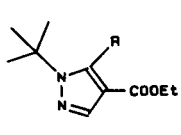
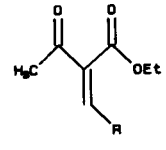
We recently reported [1a-b] the synthesis of 1-aryl-5-halo-1*H*-pyrazole-4-carboxylate esters by processes involving nonaqueous diazotization of the corresponding 5-amino esters. Carboxamides derived from the halo esters were herbicides [1a]. The corresponding 5-cyano esters were obtained by nucleophilic displacement of the 5-halo derivatives with sodium cyanide. Carboxamides derived from these cyano esters were also herbicides [2]. We wished to examine the corresponding 1-*t*-butylcyanocarboxamides for their potential herbicidal properties.

Ethyl 5-amino-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylate (**1a**) was prepared in 75% yield by the condensation of *t*-butylhydrazine with ethyl (ethoxymethylene)-cyanoacetate. Treatment of **1a** with hydrogen chloride and nitrosyl chloride in chloroform resulted in an 88% yield of the corresponding chloro ester **1b**. The yield was lower when nitrosyl chloride was used alone. Utilizing a wide variety of conditions, we found that the chlorine atom of **1b** was inert towards displacement by cyanide ion. This is apparently a steric effect, although electronic effects may also play a role.



1a R = NH_2
1b R = Cl

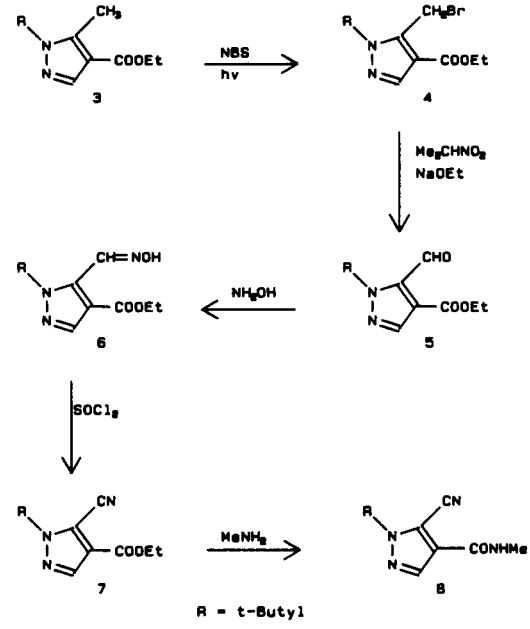


2a R = OEt
2b R = NMe_2

An alternate synthesis of the desired amides was examined (Scheme I). The reaction of ethyl 2-acetyl-3-ethoxy-2-propenoate (**2a**) [3] with *t*-butylhydrazine gave a 60:40 mixture of the two pyrazole regioisomers. The minor component was later shown to be **3**. Ethyl 2-acetyl-3-dimethylamino-2-propenoate (**2b**) was prepared in 93% yield by the condensation of ethyl acetoacetate and *N,N*-dimethylformamide dimethyl acetal. Reaction of **2b** with *t*-butylhydrazine, hydrochloride salt, yielded the desired **3** (88%) with only a trace of its regioisomer.

Bromination of **3** with *N*-bromosuccinimide under photolytic conditions gave the bromomethyl derivative **4** (85%). Attempts to dibrominate **3** using two equivalents of *N*-bromosuccinimide resulted only in the formation of **4**, apparently again due to the steric properties of the *t*-butyl group. Reaction of **4** with the sodium salt of 2-nitropropane [4] yielded the aldehyde **5** (70%). Treatment of **5** with hydroxylamine gave a 60:40 mixture of the two isomeric

Scheme I



oximes. The major isomer was obtained pure by crystallization from toluene. Ordinarily, the crude oxime mixture was dehydrated with thionyl chloride in diethyl ether, and the cyano ester **7** was obtained in 61% yield. Aminolysis with methylamine produced the desired cyano carboxamide **8** in 82% yield. The structure assigned to **8** (and thus **3** through **7**) was confirmed by X-ray diffraction analysis. The ORTEP plot is shown in Figure 1.

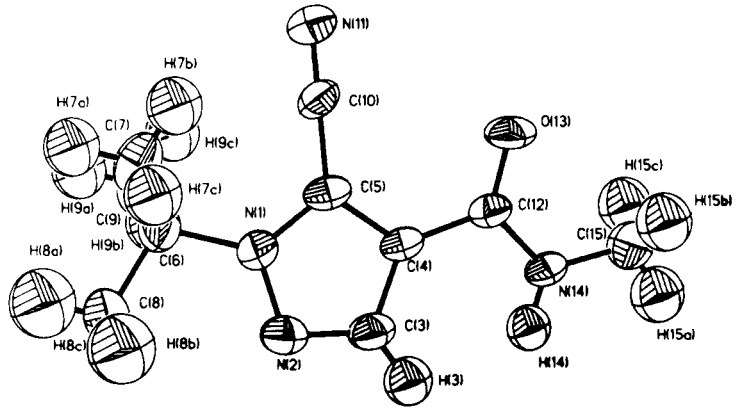


Figure 1. ORTEP plot of **8** with the numbering scheme used in the crystallographic study.

Compound **8** was crystallized from toluene in the monoclinic space group $P2_1/a$, with four molecules in a unit cell having the dimensions a = 9.896(2) Å; b = 12.761(2) Å; c = 9.550(1) Å; β = 108.57°. The calculated density was 1.198 g/cm^3. Intensities of 1768 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 0.0849 for 745 observed reflections. Table I shows unit cell atomic coordinates.

Table I

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

atom	x	y	z	U [a]
N(1)	1113(3)	74(2)	7774(3)	44(1)
N(2)	−291(3)	−65(2)	7197(3)	56(1)
C(3)	−775(3)	742(3)	6281(4)	52(1)
C(4)	336(3)	1417(2)	6256(3)	39(1)
C(5)	1543(3)	956(2)	7218(3)	42(1)
C(6)	2013(3)	−688(2)	8891(3)	52(1)
C(7)	3202(4)	−1109(3)	8344(4)	62(1)
C(8)	1055(4)	−1581(3)	9055(5)	83(2)
C(9)	2618(4)	−107(3)	10342(4)	68(1)
C(10)	2974(4)	1331(3)	7686(4)	49(1)
N(11)	4118(3)	1627(3)	8047(3)	73(1)
C(12)	293(3)	2382(2)	5402(3)	41(1)
O(13)	1384(2)	2774(2)	5261(3)	62(1)
N(14)	−1003(2)	2793(2)	4759(3)	44(1)
C(15)	−1206(3)	3768(3)	3934(4)	66(1)

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

EXPERIMENTAL

Melting points were obtained on a Mel-Temp apparatus and are uncorrected. The ^{1}H nmr spectra were determined in deuteriochloroform. Ethoxy nmr data for all ethyl esters were omitted because of their similarity.

5-Amino-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**1a**).

A solution containing 10.0 g (0.08 mole) of *t*-butylhydrazine, hydrochloride salt, 13.6 (0.08 mole) of ethyl (ethoxymethylene)cyanoacetate, and 8.2 g (0.10 mole) of anhydrous sodium acetate in 100 ml of ethanol was stirred and refluxed for 16 hours. The solution was poured into ice-water and extracted with chloroform. The organic layer was washed successively with water and saturated brine solution and dried with sodium sulfate. The solvent was removed *in vacuo*, and the mixture was distilled to yield 12.6 g (75%) of product, bp 110°/0.1 mm; ^{1}H nmr: δ 7.04 (s, 1H), 4.96 (broad, 2H), 1.32 (s, 9H).

Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.59; H, 8.15; N, 19.97.

5-Chloro-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**1b**).

Hydrogen chloride gas was bubbled into a stirred, cold solution of 25.4 g (0.12 mole) of **1a** in 150 ml of chloroform for approximately 2 minutes. Nitrosyl chloride (excess) [5] was bubbled into the solution for 5 minutes. The mixture was allowed to reach ambient temperature during 30 minutes. The solvent was removed *in vacuo*, and the mixture was distilled to yield 24.4 g (88%) of product, bp 110°/0.2 mm; ^{1}H nmr: δ 7.37 (s, 1H), 1.43 (s, 9H).

Anal. Calcd. for $C_{10}H_{15}ClN_2O_2$: C, 52.06; H, 6.55; N, 12.14. Found: C, 51.85; H, 6.38; N, 12.37.

2-Acetyl-3-(dimethylamino)-2-propenoic Acid, Ethyl Ester (**2b**).

A solution containing 60.4 g (0.46 mole) of ethyl acetoacetate, 92.4 ml (0.69 mole) of *N,N*-dimethylformamide dimethyl acetal, and about 200 mg of *p*-toluenesulfonic acid was heated on the steam bath in an open flask for 1.5 hours. The mixure was distilled to yield 79.3 g (93%) of product, bp 150°/1.0 mm.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.16; H, 7.93; N, 7.52.

1-(1,1-Dimethylethyl)-5-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3**).

A solution containing 50.0 g (0.27 mole) of **2b** and 33.6 g (0.27 mole) of *t*-butylhydrazine, hydrochloride salt in 150 ml of ethanol was stirred and refluxed for 2 hours. The solvent was removed *in vacuo*. The material was dissolved in 300 ml of diethyl ether which was washed successively with saturated sodium bicarbonate and brine solutions and dried with

sodium sulfate. The solvent was removed *in vacuo*, and the product was distilled to yield 49.7 g (88%) of product, bp 110°/1.2 mm; ^{1}H nmr: δ 7.76 (s, 1H), 2.75 (s, 3H), 1.66 (s, 9H).

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.88; H, 8.86; N, 13.50.

5-Bromomethyl-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**4**).

A suspension containing 30.0 g (0.14 mole) of **3** and 25.4 g (0.14 mole) of *N*-bromosuccinimide in 100 ml of carbon tetrachloride was stirred, refluxed, and irradiated (275 W Reflector Lamp) for 3 hours. The mixture was cooled and filtered. The organic solution was washed successively with water and saturated brine solution and dried with sodium sulfate. The solvent was removed *in vacuo* to yield 34.5 g (85%) of an oil, which could not be vacuum distilled because of thermal instability; ^{1}H nmr: δ 7.84 (s, 1H), 5.08 (s, 2H), 1.74 (s, 9H).

Anal. Calcd. for $C_{11}H_{17}BrN_2O_2$: C, 45.69; H, 5.93; N, 9.69; Br, 27.63. Found: C, 45.76; H, 5.65; N, 9.86; Br, 27.56.

1-(1,1-Dimethylethyl)-5-formyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**5**).

A solution of sodium ethoxide was prepared by dissolving 1.6 g (0.07 mole) of sodium in 50 ml of absolute ethanol. To this solution was added 8.1 g (0.09 mole) of 2-nitropropane and 20.0 g (0.07 mole) of **4** in that order. The mixture was stirred and refluxed for 2 hours. The solvent was removed *in vacuo*. The crude product was dissolved in 300 ml of diethyl ether. The solution was washed successively with water, 1*N* sodium hydroxide, and saturated brine solution and dried with sodium sulfate. The solvent was removed *in vacuo*, and the mixture was distilled to yield 11.0 g (70%) of product, bp 110°/1.6 mm; ^{1}H nmr: δ 10.58 (s, 1H), 7.86 (s, 1H), 1.69 (s, 9H).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.78; H, 7.20; N, 12.72.

1-(1,1-Dimethylethyl)-5-formyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester, Oxime (**6**).

A solution containing 7.0 g (0.031 mole) of **5** and 4.3 g (0.062 mole) of hydroxylamine, hydrochloride salt, in 40 ml of absolute ethanol was stirred at ambient temperature for 16 hours. The mixture was poured into ice-water. The solid was collected and crystallized from toluene to yield 3.0 g (41%) of product, mp 105-107°; ^{1}H nmr: δ 9.00 (broad, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 1.66 (s, 9H).

Anal. Calcd. for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.43; H, 7.21; N, 17.65.

The product above was a single isomer. The crude product was a 60:40 mixture of the two oximes, and was used directly in the preparation of **7** below.

5-Cyano-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7**).

To a cold solution of 11.0 g (0.046 mole) of **6** (crude isomer mixture) in 75 ml of diethyl ether was added dropwise 6.6 ml (0.92 mole) of thionyl chloride. The mixture was allowed to come to ambient temperature and stirred for 16 hours. Water was cautiously added, and after gas evolution ceased the layers were separated. The organic solution was washed again with water and dried with sodium sulfate. The solvent was removed *in vacuo*, and the mixture was distilled to yield 6.2 g (61%) of product, bp 124°/1.6 mm; ^{1}H nmr δ 7.90 (s, 1H), 1.79 (s, 9H).

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.90; H, 6.65; N, 18.79.

5-Cyano-1-(1,1-dimethylethyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (**8**).

A solution containing 29.0 g (0.13 mole) of **7** in 150 ml of dimethylformamide and 29 ml of 40% aqueous methylamine solution was stirred at ambient temperature for 20 hours. Starting material was still present. The mixture was heated on the steam bath and methylamine gas was bubbled in for 3 hours. The solution was poured into ice-water. The solid was collected and crystallized from ethanol to yield 22.0 g (82%) of product, mp 163-165°; ^{1}H nmr: δ 7.78 (s, 1H), 6.55 (broad, 1H), 2.95 (d, 3H), 1.76 (s, 9H).

Anal. Calcd. for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16. Found: C, 57.96; H, 6.56; N, 27.17.

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REFERENCES AND NOTES

[1a] J. R. Beck and M. P. Lynch, British Patent Application 2,149,402A (1985); [b] J. R. Beck, R. P. Gajewski, M. P. Lynch, and F. L. Wright, *J. Heterocyclic Chem.*, submitted for publication.

[2] J. R. Beck, U. S. Patent 4,589,905 (1986).

[3] L. Claisen, *Ann. Chem.*, **297**, 1 (1897).

[4] H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949).

[5] J. R. Morton and H. W. Wilcox, *Inorg. Synth.*, **4**, 48 (1953).