A New Synthesis of 1-Aryl-5-cyano-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters

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A novel conversion of 5-amino-1-aryl-1*H*-pyrazole-4-carboxylic acid, ethyl esters to the corresponding 5-cyano esters is described. The process involves nonaqueous diazotization of the amine to form the methyl thioether, which is oxidized to the methyl sulfone, which, in turn, is displaced by cyanide ion. The cyano esters are precursors to chemical hybridizing agents in wheat and barley.

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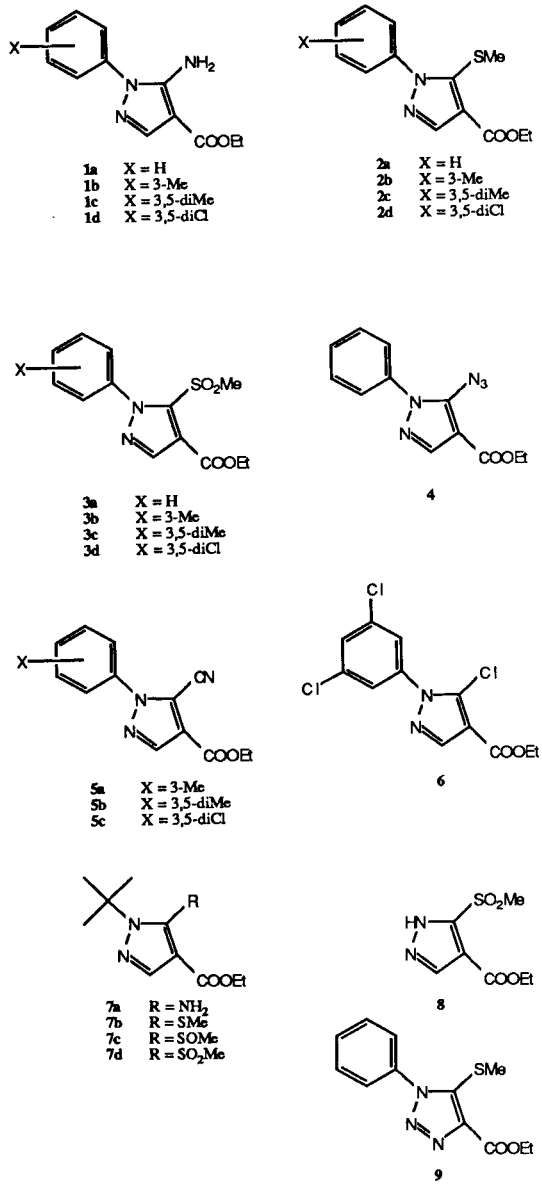
We recently reported [1a-b] the synthesis of 1-aryl-5-cyano-1*H*-pyrazole-4-carboxylic acid, ethyl esters by cyanide ion displacement of the corresponding 5-chloro esters, which were prepared from 5-amino esters by a process involving nonaqueous diazotization with nitrosyl chloride [2a-b]. Hydrolysis of the cyano esters yielded 5-(aminocarbonyl)-1-aryl-1*H*-pyrazole-4-carboxylic acids, which are chemical hybridizing agents (pollen suppressants) in wheat and barley [3]. We now wish to describe a new synthesis of these cyano ester intermediates, which involves cyanide ion displacement of the corresponding 5-methylsulfonyl derivatives.

The hybridizing agents obtained by hydrolysis of the cyano esters **5a** and **5b** were of particular interest because of their high level of activity. It was, therefore, necessary to synthesize large quantities. Unfortunately, treatment of the amino ester **1b** with nitrosyl chloride in chloroform resulted in the formation of major amounts (30-40%) of the desamino ester [2a] in addition to the expected chloro ester, and this made scale-up impossible. Similar results were encountered with the amino ester **1c**. We, therefore, investigated the potential of methylsulfonyl as the leaving group in the synthesis of **5a** and **5b**.

The conversion of arylamines to (methylthio)benzenes utilizing nonaqueous diazotization conditions has been reported. Oae and co-workers [4] utilized *t*-butyl thionitrite and Giam and Kikukawa [5] used isopentyl nitrite as diazotizing agents. In both cases, dimethyl disulfide was the solvent. We recently reported a synthesis of **2a** [2a], but the yield was only 57%. We have found that the yield of **2a** can be increased to 85% by carefully controlling the rate of addition of *t*-butyl nitrite to a solution of **1a** and dimethyl disulfide in chloroform. Oxidation of **2a** with hydrogen peroxide in acetic acid produced the methyl sulfone **3a** (90%). The leaving group potential of the methylsulfonyl function was demonstrated by reaction with azide ion in dimethylformamide, which resulted in the formation of the azido ester **4** (74%). This displacement was unsuccessful in the case of the corresponding chloro ester.

The reaction sequence was investigated for the synthesis of the desired cyano esters **5a** and **5b**. Slow addition of *t*-butyl nitrite (1.5 equivalents) to a solution of **1b** and dimethyl disulfide (2.0 equivalents) in chloroform at 55° produced **2b** (75%). The yield of desamino product in this



case was only 1-2%. Oxidation of the crude reaction mixture with hydrogen peroxide in acetic acid gave an overall two-step yield of 55% for the methyl sulfone **3b**. Treatment of **3b** with sodium cyanide (2.2 equivalents) in dimethylformamide at 80° for 35 minutes yielded the cyano ester **5a** (96%). Similarly, the amino ester **1c** was converted to **2c** (81%), which was oxidized to the sulfone **3c** (69%). Cyanide displacement gave the cyano ester **5b** (76%).

Another example involved the synthesis of the cyano ester **5c**. Nonaqueous diazotization of the amino ester **1d** in the presence of dimethyl disulfide yielded the thioether **2d** (74%). Oxidation gave the sulfone **3d** (75%), and cyanide displacement formed the cyano ester **5c** (74%). However, in this example, the nitrosyl chloride process was superior. Treatment of **1d** with nitrosyl chloride (3.5 equivalents) and gaseous hydrogen chloride in chloroform gave the chloro ester **6** (89%). Displacement with cyanide ion yielded the cyano ester **5c** (83%).

As a consequence of our investigation of many examples involving the synthesis of 1-aryl-5-cyano-1*H*-pyrazole-4-carboxylic acid, ethyl esters, we have reached the following conclusions: 1) the nitrosyl chloride process is superior with electron-withdrawing groups on the aryl, and conversely the methyl thioether route is superior with electron-donating groups present [6], 2) the nitrosyl chloride reaction gives higher yields in the presence of hydrogen chloride and 3) cyanide displacement of methylsulfonyl is much faster than chloro, as is usually the case.

Two other examples were investigated during the course of this work. Treatment of the *t*-butyl pyrazole derivative **7a** [7] under conditions which led to the thioethers **2a-d**, yielded **7b** (74%). Oxidation of **7b** with hydrogen peroxide in acetic acid gave the methyl sulfone **8** (60%) with loss of the *t*-butyl group. Compound **7b** was, however, readily oxidized to the methylsulfinyl ester **7c** (92%) with peracetic acid in methylene chloride in 30 minutes at 8°. Further oxidation to the sulfone **7d** (70%) with peracetic acid required several days at ambient temperature. Attempted displacement of either the methylsulfinyl or methylsulfonyl functions by cyanide ion in dimethylformamide at elevated temperature was unsuccessful as was the case with the corresponding chloro ester [7].

Finally, 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid, ethyl ester [8] was allowed to react with *t*-butyl nitrite and dimethyl disulfide under the usual conditions, and the methyl thioether **9** was obtained in 71% yield. Although several other 1-aryl-1,2,3-triazole amino esters were examined, the reaction was not as general as in the case of the pyrazole amino esters, and the conversions ordinarily resulted in lower yields.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Ethyl (ethoxymethylene)cyanoacetate, *t*-butyl nitrite, dimethyl disulfide, *m*-tolylhydrazine and 3,5-dichlorophenylhydrazine were commercially available (Aldrich Chemical Co.). All chromatographic separations (hplc) were with Woelm 04530 silica gel using an FMI (RP SY) standard pump.

5-(Methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**2a**).

A solution containing 42.4 g (0.183 mole) of **1a** [9] and 34.55 g (0.367 mole) of dimethyl disulfide in 240 ml of chloroform was cooled to 10°. *t*-Butyl nitrite (28.37 g, 0.275 mole) was added to a dropping funnel, and one quarter was added rapidly to the cold solution. Reaction initiation commenced at 15°. The temperature was controlled at about 30° by the slow addition of the remaining *t*-butyl nitrite. The mixture was stirred at ambient temperature for 16 hours. The solution was washed twice with water, once with saturated brine and dried by passing through PS filter paper. The solvent was removed *in vacuo*, and the product was crystallized from ethanol-water to yield 40.56 g (85%) of **2a**, mp 56-57.5°, lit [2a] mp 58-59°.

5-(Methylsulfonyl)-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3a**).

A solution of 4.0 g (15.3 mmoles) of **2a** in 10 ml of 30% hydrogen peroxide and 20 ml of acetic acid was heated at steam bath temperature for 1.5 hours. The mixture was poured into ice-water. The solid was collected and crystallized from toluene-hexane to yield 4.05 g (90%) of **3a**, mp 133-134°; nmr (deuteriochloroform): δ 8.16 (s, 1H), 7.3-7.6 (m, 5H), 4.40 (q, 2H), 3.48 (s, 3H), 1.44 (t, 3H).

Anal. Calcd. for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52. Found: C, 53.07; H, 5.03; N, 9.57.

5-Azido-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**4**).

A solution containing 8.44 g (28.7 mmoles) of **3a** and 3.73 g (57.0 mmoles) of sodium azide in 60 ml of dimethylformamide was stirred and heated at 70° for 5 hours. The mixture was poured into ice water. The solid was collected and crystallized from ethanol-water to yield 5.48 g (74%) of **4**, mp 74-75°; ir (potassium bromide): 2140, 1720 cm^{-1}; nmr (deuteriochloroform): δ 7.97 (s, 1H), 7.35-7.65 (m, 5H), 4.38 (q, 2H), 1.41 (t, 3H); ms: m/e 257 (M^+).

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.11; H, 4.49; N, 27.00.

1-(3-Methylphenyl)-5-(methylthio)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**2b**).

A solution containing 54.2 g (0.221 mole) of **2a** [10] and 41.45 g (0.440 mole) of dimethyl disulfide in 300 ml of chloroform was stirred at ambient temperature. *t*-Butyl nitrite (34.0 g, 0.330 mole) was placed in a dropping funnel, and one-third was added rapidly. The solution was slowly heated, and the reaction initiated at about 50°. The remaining *t*-butyl nitrite was added during 30 minutes at a rate to maintain the temperature at about 50°. The reaction was refluxed for 15 minutes. The solution was washed with water and saturated brine and dried by passing through PS filter paper. The solvent was removed *in vacuo* to yield 57.67 g. A 10.0 g portion was chromatographed (hplc) with hexane-ethyl acetate (3:1) as eluent. The yield was 7.92 g (75%) of **2b** as an oil; nmr (deuteriochloroform): δ 8.14 (s, 1H), 7.1-7.4 (m, 4H), 4.35 (q, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.41 (t, 3H); ms: m/e 276 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.96; H, 5.58; N, 10.37.

1-(3-Methylphenyl)-5-(methylsulfonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3b**).

An 11.2 g portion of the crude product above was dissolved in 25 ml of 30% hydrogen peroxide and 50 ml of acetic acid. The mixture was heated at steam bath temperature for 1 hour. The solution was poured into ice water with rapid stirring. The solid was collected to yield 10.4 g, mp 95-101°. Crystallization from ethanol gave 6.9 g (55%) of **3b**, mp 104.5-106°; nmr (deuteriochloroform): δ 8.14 (s, 1H), 7.1-7.4 (m, 4H), 4.41 (q, 2H), 3.46 (s, 3H), 2.45 (s, 3H), 1.43 (t, 3H); ms: m/e 308 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08. Found: C, 54.75; H, 5.47; N, 8.93.

5-Cyano-1-(3-methylphenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**5a**).

A solution of 4.03 g (13.1 mmoles) of **3b** and 1.41 g (28.8 mmoles) of finely powdered sodium cyanide in 30 ml of dimethylformamide was stirred and heated at 80° for 35 minutes. The mixture was poured into 150 ml of ice water and allowed to crystallize to yield 3.17 g (96%) of **5a**, mp 54-56°; nmr (deuteriochloroform): δ 8.19 (s, 1H), 7.25-7.5 (m, 4H), 4.43 (q, 2H), 2.47 (s, 3H), 1.45 (t, 3H); ms: m/e 255 (M^+).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.18; H, 5.10; N, 16.72.

5-Amino-1-(3,5-dimethylphenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**1c**).

A solution containing 37.9 g (0.224 mole) of ethyl (ethoxymethylene)-cyanoacetate, 38.65 g (0.224 mole) of 3,5-dimethylphenylhydrazine, hydrochloride salt [11], and 36.7 g (0.448 mole) of sodium acetate in 300 ml of ethanol was stirred and refluxed for 20 hours. The mixture was poured into 1000 ml of ice water with vigorous stirring. The solid was collected and crystallized from ethanol-water (charcoal treatment) to give 40.8 g (70%) of **1c**, mp 113-114°.

Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 65.05; H, 6.27; N, 15.84.

1-(3,5-Dimethylphenyl)-5-(methylthio)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**2c**).

A solution containing 30.6 g (0.118 mole) of **1c** and 22.2 g (0.236 mole) of dimethyl disulfide in 180 ml of chloroform was stirred at ambient temperature. *t*-Butyl nitrite (18.3 g, 0.177 mole) was placed in a dropping funnel, and one-fourth was added rapidly. The reaction initiated and the temperature rose to 35°. Another quarter of the *t*-butyl nitrite was added, and the temperature rose to about 55°. The remaining nitrite was added at a rate to maintain the temperature at about 50°. The reaction was stirred at ambient temperature for 16 hours. The solution was washed twice with water and once with saturated brine and passed through PS filter paper. The solvent was removed *in vacuo* to yield 34.5 g. A 10.2 g portion was chromatographed (hplc) using hexane-ethyl acetate (3:1) as eluent. The yield was 8.23 g (81%) of **2c** as an oil; ir (neat): 1720 cm^{-1}; nmr (deuteriochloroform): δ 8.12 (s, 1H), 7.10 (s, 3H), 4.35 (q, 2H), 2.38 (s, 9H), 1.40 (t, 3H).

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.70; H, 6.69; N, 10.04.

1-(3,5-Dimethylphenyl)-5-(methylsulfonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3c**).

A solution of 7.31 g (25.2 mmoles) of **2c** in 15 ml of 30% hydrogen peroxide and 30 ml of acetic acid was heated at steam bath temperature for 1.75 hours. The product crystallized and was collected to yield 5.6 g (69%) of **3c**, mp 120-121.5°; ir (potassium bromide): 1735 cm^{-1}; nmr (deuteriochloroform): δ 8.07 (s, 1H), 7.14 (s, 1H), 7.01 (s, 2H), 4.40 (q, 2H), 3.44 (s, 3H), 2.35 (s, 6H), 1.40 (t, 3H).

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.89; H, 5.63; N, 8.69. Found: C, 56.13; H, 5.34; N, 8.84.

5-Cyano-1-(3,5-dimethylphenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**5b**).

A solution containing 4.97 g (15.4 mmoles) of **3c** and 1.89 g (38.6 mmoles) of finely powdered sodium cyanide in 35 ml of dimethylformamide was stirred and heated at 80-90° for 30 minutes. The mixture was poured into 100 ml of ice water. The solid was collected and crystallized from ethanol-water to give 3.14 g (76%) of **5b**, mp 83.5-84.5°; nmr (deuteriochloroform): δ 8.17 (s, 1H), 7.28 (s, 2H), 7.14 (s, 1H), 4.41 (q, 2H), 2.40 (s, 6H), 1.41 (t, 3H).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.60; N, 15.60. Found: C, 66.64; H, 5.54; N, 15.34.

5-Amino-1-(3,5-dichlorophenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**1d**).

A solution containing 25.0 g (0.117 mole) of 3,5-dichlorophenylhydrazine, hydrochloride salt, 18.6 g (0.110 mole) of ethyl (ethoxymethylene)-cyanoacetate and 18.0 g (0.220 mole) of sodium acetate in 200 ml of ethanol was stirred and refluxed for 20 hours. The mixture was poured into 700 ml of ice water. The solid was collected and crystallized from ethanol to yield 28.5 g (86%) of **1d**, mp 157-158°.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3O_2$: C, 48.02; H, 3.69; N, 14.00. Found: C, 47.81; H, 3.58; N, 14.22.

1-(3,5-Dichlorophenyl)-5-(methylthio)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ether (**2d**).

A suspension of 14.21 g (47.4 mmoles) of **1d** and 8.92 g (94.9 mmoles) of dimethyl disulfide in 140 ml of chloroform was stirred at ambient temperature. *t*-Butyl nitrite (7.27 g, 70.6 mmoles) was placed in a dropping funnel, and about half was added rapidly to the reaction mixture. The reaction commenced, and the temperature rose to 50°. The remaining nitrite was added dropwise at a rate, which maintained the temperature at about 50°. The clear solution was stirred at ambient temperature for 16 hours. The mixture was washed twice with water and once with saturated brine and dried by passing through PS filter paper. The solvent was removed *in vacuo*. The crude oil was chromatographed (hplc) with hexane-ethyl acetate (3.5:1) as eluent. The yield was 11.55 g (74%) of **2d**, mp 70-72°; nmr (deuteriochloroform): δ 8.12 (s, 1H), 7.3-7.65 (m, 3H), 4.35 (q, 2H), 2.43 (s, 3H), 1.38 (t, 3H).

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O_2S$: C, 47.14; H, 3.65; N, 8.46. Found: C, 47.35; H, 3.74; N, 8.65.

1-(3,5-Dichlorophenyl)-5-(methylsulfonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3d**).

A suspension of 9.29 g (28.1 mmoles) of **2d** in 20 ml of 30% hydrogen peroxide and 40 ml of acetic acid was heated at steam bath temperature. The solution cleared in 10 minutes, and then a solid commenced forming. The mixture was heated for another hour. Enough acetic acid was added to obtain a clear hot solution, and the mixture was filtered and cooled to obtain 7.6 g (75%) of **3d**, mp 179-181°; nmr (DMSO-d_6): δ 8.26 (s, 1H), 7.75-7.9 (m, 3H), 4.31 (q, 2H), 3.55 (s, 3H), 1.28 (t, 3H).

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O_4S$: C, 42.99; H, 3.33; N, 7.71. Found: C, 43.15; H, 3.44; N, 7.70.

5-Cyano-1-(3,5-dichlorophenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**5c**).

A solution containing 6.97 g (19.2 mmoles) of **3d** and 2.35 g (48.0 mmoles) of finely powdered sodium cyanide in 60 ml of dimethylformamide was stirred and heated at 80° for 30 minutes. The mixture was poured into 200 ml of ice water. The solid was collected and crystallized from ethanol (charcoal treatment) to yield 4.38 g (74%) of **5c**, mp 101-103°; ir (potassium bromide): 2240, 1725 cm^{-1}; nmr (deuteriochloroform): δ 8.17 (s, 1H), 7.67 (s, 2H), 7.50 (s, 1H), 4.41 (q, 2H), 1.40 (t, 3H).

Anal. Calcd. for $C_{13}H_9Cl_2N_3O_2$: C, 50.35; H, 2.93; N, 13.55. Found: C, 50.32; H, 3.03; N, 13.37.

5-Chloro-1-(3,5-dichlorophenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**6**).

Hydrogen chloride gas was bubbled into a suspension of 18.1 g (60.3 mmoles) of **1d** in 300 ml of chloroform for 2-3 minutes. The solution was cooled to 5° and liquid nitrosyl chloride (13.8 g, 0.211 mole) [12] was added. The solution was allowed to warm to ambient temperature for 1 hour. The mixture was heated to reflux for 10 minutes in an open flask to remove excess nitrosyl chloride. The solution was washed with saturated sodium bicarbonate solution, water and saturated brine and dried by passing through PS filter paper. The solvent was removed *in vacuo*, and the product was crystallized from ethanol to give 17.07 g (89%) of **6**, mp 104-105°; nmr (deuteriochloroform): δ 7.93 (s, 1H), 7.25-7.45 (m, 3H), 4.27 (q, 2H), 1.37 (t, 3H).

Anal. Calcd. for $C_{12}H_9Cl_3N_2O_2$: C, 45.10; H, 2.84; N, 8.77. Found: C, 45.34; H, 2.65; N, 8.93.

5-Cyano-1-(3,5-dichlorophenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**5c**).

A solution containing 17.02 g (0.053 mole) of **6** and 6.53 g (0.133 mole) of finely powdered sodium cyanide in 130 ml of dimethylformamide was heated at 100° for 2.5 hours. The mixture was poured into 400 ml of ice water. The solid was collected and crystallized from ethanol to yield 13.55 g (83%) of **5c**, mp 105-107° (identical to **5c** prepared above).

1-(1,1-Dimethylethyl)-5-(methylthio)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7b**).

A solution containing 29.3 g (0.139 mole) of **7a** [7] and 26.15 g (0.278 mole) of dimethyl disulfide in 200 ml of chloroform was stirred and cooled to 5°. *t*-Butyl nitrite (21.5 g, 0.208 mole) was placed in a dropping funnel, and one-third was added rapidly to the cold solution. The mixture was allowed to warm, and the reaction initiated at 20° with the temperature rising to about 50°. The remaining nitrite was added dropwise at a rate to maintain the temperature at about 50° with external cooling. The solution was stirred at ambient temperature for 16 hours. The mixture was washed twice with water and once with saturated brine and was dried by passing through PS filter paper. The solvent was removed *in vacuo*. The residue was distilled, and the product (27.1 g) was collected at 110-115°/0.25 mm. This material was of sufficient purity for use in the oxidations described below. A 5.0 g portion was chromatographed (hplc) with hexane-ethyl acetate (3:1) as eluent to yield 4.6 g (74%) of **7b** as an oil; nmr (deuteriochloroform): δ 7.88 (s, 1H), 4.31 (q, 2H), 2.50 (s, 3H), 1.79 (s, 9H), 1.36 (t, 3H); ms: m/s 242 (M^+).

Anal. Calcd. for $C_{11}H_{18}N_2O_2S$: C, 54.52; H, 7.49; N, 11.56. Found: C, 54.73; H, 7.50; N, 11.36.

5-(Methylsulfonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**8**).

A solution containing 10.0 g (41.3 mmoles) of **7b** in 25 ml of 30% hydrogen peroxide and 50 ml of acetic acid was heated at steam bath temperature for 1.5 hours. The mixture was poured into 300 ml of ice water, from which a precipitate slowly formed. The solid was collected and crystallized from toluene to give 5.38 g (60%) of **8**, mp 157.5-159°; nmr (DMSO-d_6): δ 8.60 (s, 1H), 4.26 (q, 2H), 3.40 (s, 3H), 1.28 (t, 3H); ms: m/e 218 (M^+).

Anal. Calcd. for $C_7H_{10}N_2O_4S$: C, 38.53; H, 4.62; N, 12.84. Found: C, 38.74; H, 4.41; N, 12.96.

1-(1,1-Dimethylethyl)-5-(methylsulfinyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7c**).

To a cold solution of 4.40 g (0.018 mole) of **7b** in 40 ml of dichloromethane was added 2.66 g (0.025 mole) of sodium carbonate. Peracetic acid (35%, 5.0 g, 0.023 mole) was added dropwise during 15 minutes while maintaining the temperature below 8°. The reaction was stirred in the cold for 1 hour. Water (100 ml) and dichloromethane (100 ml) were added. The organic solution was washed with saturated sodium bicarbonate and brine solutions and dried by passing through PS filter paper. The solvent was removed *in vacuo* to yield 4.26 g (92%) of **7c** as an oil; nmr (deuteriochloroform): δ 7.88 (s, 1H), 4.35 (q, 2H), 3.26 (s, 3H), 1.74 (s, 9H), 1.36 (t, 3H); ms: m/e 258 (M^+).

Anal. Calcd. for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84. Found: C, 51.39; H, 7.03; N, 10.94.

1-(1,1-Dimethylethyl)-5-(methylsulfonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7d**).

Peracetic acid (35%, 13.03 g, 0.060 mole) was added to a cold solution containing 4.93 g (0.020 mole) of **7b** and 7.0 g (0.066 mole) of sodium carbonate in 45 ml of dichloromethane as in the case of **7c** above. The mixture was stirred at ambient temperature for 24 hours. Peracetic acid (2.17 g) and sodium carbonate (1.17 g) were added and the mixture was stirred at ambient temperature for 3 days. The reaction was treated as with **7c** to yield a crude product, which was crystallized from cyclohexane to give 3.86 g (70%) of **7d**, mp 88-89°; nmr (deuteriochloroform): δ 7.72 (s, 1H), 4.33 (q, 2H), 3.47 (s, 3H), 1.79 (s, 9H), 1.38 (t, 3H); ms: m/e 274 (M^+).

Anal. Calcd. for $C_{11}H_{18}N_2O_4S$: C, 48.16; H, 6.61; N, 10.21. Found: C, 48.43; H, 6.69; N, 10.13.

5-(Methylthio)-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic Acid, Ethyl Ester (**9**).

To a solution containing 0.84 g (3.6 mmoles) of 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid, ethyl ester [8] and 0.68 g (7.2 mmoles) of dimethyl disulfide in 10 ml of chloroform was added 0.56 g (5.4 mmoles) of *t*-butyl nitrite at ambient temperature. A vigorous reaction ensued, and the mixture was stirred at ambient temperature for 1 hour. The solution was extracted twice with water and once with saturated brine and dried by passing through PS filter paper. The solvent was removed *in vacuo*. The crude oil was chromatographed (hplc) with hexane-ethyl acetate (3:1) as eluent to give 0.67 g (71%) of **9** as an oil; nmr (deuteriochloroform): δ 7.5-7.7 (m, 5H), 4.48 (q, 2H), 2.38 (s, 3H), 1.47 (t, 3H); ms: m/e 263 (M^+).

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.46; H, 4.77; N, 16.23.

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[6] This is because the nitrosyl chloride method leads to desamino side product, especially when electron donating substituents are present. This is not a problem with the methylthio route, which does, however, require an additional step in the process.

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