Alkylation Studies with 5-Cyano-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester

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5-Cyano-1*H*-pyrazole-4-carboxylic acid, ethyl ester (**1**) was regioselectively alkylated at N-1 by tertiary carbocations utilizing sulfuric acid catalysis and relatively mild conditions. In the presence of boron trifluoride, the alkylation occurred regioselectively at N-2. Reaction of **1** with alkyl halides under basic conditions resulted in mixtures of the two isomers with alkylation at N-2 predominating.

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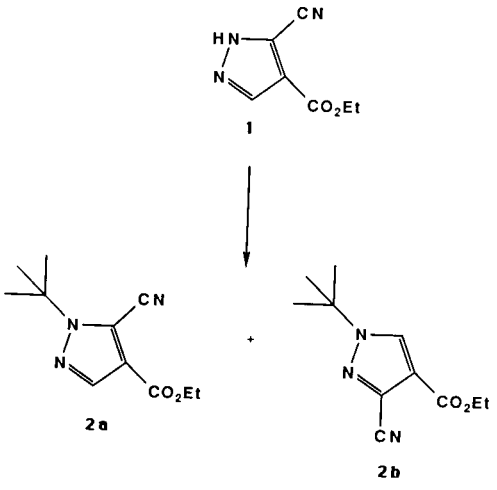
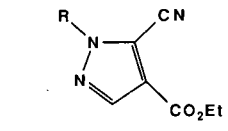
We recently reported [1] the synthesis of 5-cyano-1*H*-pyrazole-4-carboxylic acid, ethyl ester (**1**) and its regioselective alkylation with isobutylene to yield 5-cyano-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic acid, ethyl ester (**2a**) (Scheme I). This ester was converted to the corresponding *N*-methylcarboxamide, which has shown significant herbicidal activity [2].

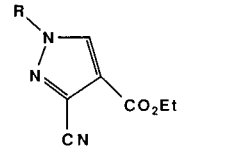
Scheme I



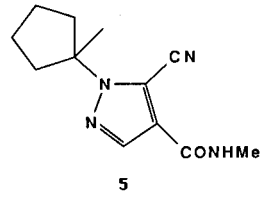
The alkylation conditions involved treatment of **1** with two equivalents of isobutylene and 0.3 equivalent of *p*-toluenesulfonic acid monohydrate in acetonitrile at 80-85° for 24 hours in a pressure vessel. Regioselectivity (**2a:2b**) was greater than 90:1. Lewis acids were also examined in the reaction, and the ratios of **2a:2b** formed were: aluminum chloride (1:99); boron trifluoride (1:23); stannic chloride (1:2); zinc chloride (10:1). These results indicate that stronger Lewis acids prefer to coordinate or bind with the long electron pair at N-1 and thereby provide alkylation at N-2. It is interesting to note that the amount of **2b** formed is in direct correlation with Lewis acid strength in related reactions [3]. We now wish to report further examples of this tertiary carbocation alkylation of **1**, as well as several alkylations involving the sodium salt of **1** as a nucleophile.



3a R=1-Ethyl-1-methylpropyl
3b R=1,1-Dimethylbutyl
3c R=1,1-Dimethylpropyl
3d R=1,1-Diethylpropyl
3e R=1-Methylcyclopentyl
3f R=Cyclopentyl
3g R=Cyclohexyl
3h R=Methyl



4a R=1-Ethyl-1-methylpropyl
4b R=1,1-Dimethylpropyl
4c R=Cyclopentyl
4d R=Cyclohexyl
4e R=Methyl



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With more highly substituted olefins, no reaction occurred under conditions utilized in the formation of **2a**. Higher temperatures were necessary to initiate reaction, and under these conditions regioselectivity was lost and yields decreased. For example, the reaction of **1** with 2-ethyl-1-butene and catalytic *p*-toluenesulfonic acid in acetonitrile at 120° resulted in the formation of the two isomers **3a** (22%) and **4a** (30%).

We, therefore, investigated sulfuric acid as a potential catalyst. 2-Methyl-1-pentene was allowed to react with **1** in acetonitrile and catalytic sulfuric acid at 120° for 8 hours. Regioselectivity was obtained, and the product isolated was **3b** (50%). No trace of the corresponding 3-cyano ester was detected, but unchanged **1** was present.

It was noted that related alkylations of **1** were actually occurring at ambient temperature, but were extremely slow due to the low solubility of **1** in acetonitrile. Since earlier work had shown that acetonitrile was essential for the reaction, we examined mixed solvents, in order to increase the solubility of **1**. A clear solution containing 2-methyl-2-butene, **1** and catalytic sulfuric acid in dichlo-

romethane-acetonitrile (4:1) was stirred at ambient temperature for 20 hours. Thin layer chromatography showed a single product in addition to unreacted **1**. The mixture was refluxed for 24 hours, but the thin layer chromatogram did not change. The product was isolated and identified as **3c** (64%). No attempt was made to recover unreacted **1**. Similarly prepared from 3-ethyl-2-pentene and 1-methylcyclopentene at ambient temperature were **3d** (59%) and **3e** (90%), respectively. The latter reaction was complete within two hours, and **3e** was characterized by conversion to the corresponding *N*-methylcarboxamide **5**. The regioselective synthesis of **3b, 3c, 3d,** and **3e** which involved sulfuric acid catalysis, appears to involve an equilibrium process between the products and starting pyrazole **1**, although this was not proved unequivocally.

The ability of strong Lewis acids to reverse the regioselectivity was examined using boron trifluoride. The reaction of 2-ethyl-1-butene (two equivalents) with **1** and boron trifluoride (two equivalents) [4] in acetonitrile at 90° for 17 hours led to the formation of **4a** (83%). Similarly prepared from 2-methyl-2-butene was **4b** (70%). No 5-cyano ester was detected in either case.

The alkylations described above failed with olefins incapable of forming tertiary carbocations. For this reason, direct alkylation of **1** under basic conditions was examined. Treatment of the sodium salt of **1** with cyclopentyl bromide in dimethyl sulfoxide at steam bath temperature for 24 hours yielded a mixture of **3f** (13%) and **4c** (56%). The same reaction with cyclohexyl bromide required 96 hours and resulted in low yields of **3g** (6%) and **4d** (18%). Similar treatment with methyl iodide for 24 hours gave a mixture of **3h** (17%) and **4e** (51%). In each case, the ratio of 3-cyano ester to 5-cyano ester was in the range of 3-4:1.

Assignment of structure in the various alkylations described above was arrived at by comparison of their ^{1}H nmr spectra in two solvents. Elguera and co-workers [5] reported ^{1}H nmr solvent shifts involving a series of 1-methyl and 1-phenyl substituted pyrazoles. A significant downfield shift (.18-.56 ppm) was noted for a proton at C-5 in DMSO-d_6 compared to deuteriochloroform. The corresponding shift for a proton at C-3 was either negligible or slightly upfield. Similar solvent shifts were observed by Timmermans and co-workers [6] in a series of 1,1′-didimethylbipyrazoles. In our work we observed a downfield C-3 proton shift (.07-.20 ppm) for the 5-cyano esters (Table I) and a more substantial downfield C-5 proton shift (.58-.75 ppm) for the 3-cyano esters (Table II). In addition, we were able to utilize an unusual bioassay to confirm our structural assignments. Conversion of the cyano esters **3a-h** to the corresponding *N*-methylcarboxamides, as in the case of **5**, led to compounds which showed herbicidal activity [2]. Conversion of **4a-e** to their corresponding *N*-methylcarboxamides resulted in compounds with no herbicidal activity.

Table I

Ring Proton Solvent Shifts for 1-Alkyl-5-cyano-1*H*-pyrazole-4-carboxylate Esters

Compound	Pyrazole Proton Shift (ppm) $CDCl_3$	DMSO-d_6	Δ δ
3a	7.91	8.11	.20
3b	7.91	8.11	.20
3c	7.90	8.06	.16
3d	7.93	8.13	.20
3e	7.90	8.08	.18
3f	7.99	8.06	.07
3g	7.98	8.15	.17
3h	7.98	8.11	.13

Table II

Ring Proton Solvent Shifts for 1-Alkyl-3-cyano-1*H*-pyrazole-4-carboxylate Esters

Compound	Pyrazole Proton Shift (ppm) $CDCl_3$	DMSO-d_6	Δ δ
4a	8.04	8.62	.58
4b	8.04	8.66	.62
4c	8.05	8.67	.62
4d	8.06	8.81	.75
4e	7.95	8.58	.63

In conclusion, cyano ester **1** was regioselectively alkylated at N-1 by tertiary carbocations under relatively mild conditions using sulfuric acid as catalyst. In the presence of boron trifluoride, regioselective alkylation occurred at N-2 indicating strong coordination or, more likely, actual bond formation with the strong Lewis acid at N-1. These results led us to conclude that **1** prefers to exist as the tautomer with its lone pair electrons at N-1. Further support for this hypothesis was demonstrated by alkylation of **1** under basic conditions, wherein substitution at N-2 predominated over N-1 by a factor of 3-4:1.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Woelm 04530 silica gel and an FMI (RP SY) standard pump were used in all chromatographic separations (hplc). All ^{1}H nmr spectra were determined on a Bruker WM-250 nmr spectrometer. All high temperature reactions were carried out using pressure tubes with Acethred (Ace Glass, Inc.). All olefins were commercially available from Aldrich Chemical Company or Wiley Organics.

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

A suspension of 6.77 g (0.041 mole) of **1** [1], 6.9 g (0.082 mole) of 2-ethyl-1-butene and 100 mg of *p*-toluenesulfonic acid in 20 ml of

acetonitrile was heated in a sealed tube at 120° for 26 hours. The cooled solution was filtered and evaporated *in vacuo* to yield 8.88 g of crude product. Chromatography (hplc) with hexane-ethyl acetate (4:1) as eluent yielded 2.28 g (22%) of **3a** as an oil.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.45; H, 7.53; N, 16.57.

A slower moving product was collected to yield 3.07 g (30%) of **4a** as an oil.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.67; H, 7.81; N, 16.66.

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

A suspension of 6.0 g (0.036 mole) of **1**, 6.1 g (0.073 mole) of 2-methyl-1-pentene and 5 drops of sulfuric acid in 15 ml of acetonitrile was heated in a sealed tube at 120° for 8 hours. The solvent was removed *in vacuo*, and the crude product was chromatographed (hplc) with hexane-ethyl acetate (4:1) as eluent to give 4.57 g (50%) of **3b** as an oil.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.70; H, 7.47; N, 16.76.

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

To a cold suspension containing 8.0 g (0.048 mole) of **1** and 6.8 g (0.097 mole) of 2-methyl-2-butene in 40 ml of dichloromethane and 10 ml of acetonitrile was added dropwise 4.7 g (0.048 mole) of sulfuric acid at a rate to maintain the temperature below 10°. The solution cleared after several minutes and was stirred in the cold for 30 minutes and at ambient temperature for 20 hours. Since starting **1** was still present, the mixture was heated to reflux for 24 hours. The cooled solution was washed twice with 2*N* sodium hydroxide and once with saturated brine solution. The solvent was dried with sodium sulfate and removed *in vacuo*. The crude product was chromatographed (hplc) with hexane-ethyl acetate (3:1) as eluent to yield 7.2 g (64%) of **3c** as an oil.

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 61.47; H, 7.42; N, 18.08.

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

Sulfuric acid (4.7 g, 0.048 mole) was added dropwise to a cold suspension of 8.0 g (0.048 mole) of **1** and 9.5 g (0.097 mole) of 3-ethyl-2-pentene in 40 ml of dichloromethane and 10 ml of acetonitrile, while maintaining the temperature below 10°. The clear solution was stirred in the cold for 30 minutes and at ambient temperature for 16 hours. Dichloromethane (100 ml) was added, and the mixture was washed twice with 2*N* sodium hydroxide and once with saturated brine solution. The solvent was dried with sodium sulfate and removed *in vacuo*. The crude product was chromatographed (hplc) with hexane-ethyl acetate (4:1) as eluent to yield 6.3 g (59%) of **3d** as an oil.

Anal. Calcd. for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96. Found: C, 64.09; H, 7.98; N, 16.26.

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

To a cold suspension containing 32.0 g (0.194 mole) of **1** and 31.8 g (0.393 mole) of 1-methylcyclopentene in 160 ml of dichloromethane and 40 ml of acetonitrile was added dropwise 7.0 g (0.071 mole) of sulfuric acid at a rate to maintain the temperature below 10°. The clear solution was stirred in the cold for 30 minutes and at ambient temperature for 2 hours. The solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate, which was washed twice with 2*N* sodium hydroxide and twice with saturated brine solution. The organic layer was dried with sodium sulfate and removed *in vacuo* to yield 43.0 g (90%) of **3e** as an oil. This material was of sufficient purity (nmr and tlc) for direct conversion to the carboxamide **5** below.

5-Cyano-*N*-methyl-1-(1-methylcyclopentyl)-1*H*-pyrazole-4-carboxamide (**5**).

A solution containing 43.0 g (0.174 mole) of **3e** obtained above in 300 ml of ethanol and 90 ml (1.044 mole) of 40% aqueous methylamine solution was stirred and heated to reflux for 3 hours. Water was added and the hot solution was filtered and allowed to crystallize to give 29.5 g (73%) of **5**, mp 146-148°; ^{1}H nmr (deuteriochloroform): δ 7.81 (s, 1H), 3.00 (d, 3H), 2.43 (m, 2H), 2.12 (m, 2H), 1.76 (m, 4H), 1.65 (s, 3H).

Anal. Calcd. for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 61.85; H, 6.91; N, 24.07.

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

A mixture containing 7.5 g (0.045 mole) of **1**, 7.5 g (0.089 mole) of 2-ethyl-1-butene and 12.7 g (0.089 mole) of boron trifluoride etherate in 5 ml of acetonitrile was heated in a sealed tube at 90° for 17 hours. The solvent was removed *in vacuo*, and the crude product was chromatographed (hplc) with hexane-ethyl acetate (4:1) as eluent to yield 9.3 g (83%) of **4a** as an oil.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.41; H, 7.58; N, 16.69.

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

A suspension of 5.0 g (0.030 mole) of **1**, 4.2 g (0.060 mole) of 2-methyl-2-butene and 4.3 g (0.030 mole) of boron trifluoride etherate in 15 ml of acetonitrile was heated in a sealed tube at 120° for 16 hours. The solvent was removed *in vacuo*, and the crude product was chromatographed (hplc) with hexane-ethyl acetate (4:1) as eluent to give 4.95 g (70%) of **4b** as an oil.

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 60.98; H, 7.19; N, 17.69.

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

To a solution containing 8.0 g (0.048 mole) of **1** in 40 ml of dimethyl sulfoxide was added portionwise 1.3 g (0.053 mole) of 97% sodium hydride. The solution was stirred at ambient temperature for 30 minutes. Cyclopentyl bromide (8.7 g, 0.058 mole) was added, and the solution was heated at steam bath temperature for 24 hours. The mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed twice with 2*N* sodium hydroxide and once with saturated brine solution and dried with magnesium sulfate. The solvent was removed *in vacuo*. Chromatography (hplc) with hexane-ethyl acetate (10:1) as eluent yielded 1.5 g (13%) of **3f** as an oil.

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.67; H, 6.46; N, 18.02.

A slower moving product was collected to yield 6.3 g (56%) of **4c** as an oil.

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.54; H, 6.28; N, 17.75.

5-Cyano-1-cyclohexyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3g**) and 3-Cyano-1-cyclohexyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**4d**).

The sodium salt was prepared as above from 8.0 g of **1**. Cyclohexyl bromide (9.5 g, 0.058 mole) was added, and the mixture was heated at steam bath temperature for 96 hours. Work-up was identical to the cyclopentyl case. Chromatography (hplc) with hexane-ethyl acetate (7:1) as eluent yielded 0.71 g (6%) of **3g**, mp 75-77°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.07; H, 6.94; N, 16.81.

A slower moving product was collected to yield 2.17 g (18%) of **4d**, mp 38-39°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.93; H, 7.04; N, 16.93.

5-Cyano-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3h**) and 3-Cyano-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**4e**).

The sodium salt was prepared as above from 8.0 g of **1**. Methyl iodide (8.2 g, 0.058 mole) was added, and the mixture was heated at steam bath temperature for 24 hours. Work-up was identical to the two examples above. Chromatography (hplc) with hexane-ethyl acetate (5:1) as eluent yielded 1.5 g (17%) of **3h**, mp 32-34°; ^{1}H nmr (deuteriochloroform): δ 7.98 (s, 1H), 4.38 (q, 2H), 4.10 (s, 3H), 1.38 (t, 3H).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.43; H, 5.02; N, 23.38.

A slower moving product was collected to yield 4.4 g (51%) of **4e**, mp 91-93°; ^{1}H nmr (deuteriochloroform): δ 7.95 (s, 1H), 4.35 (q, 2H), 4.00 (s, 3H), 1.39 (t, 3H).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.92; H, 5.06; N, 23.64.

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