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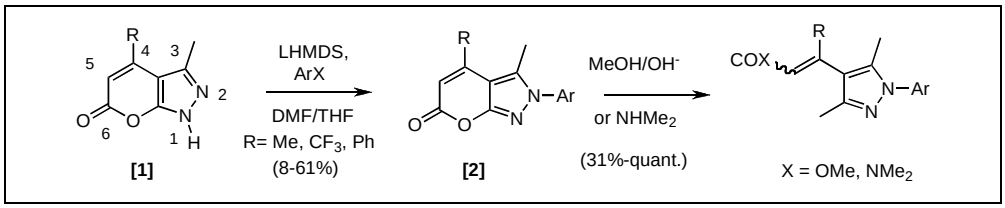

Novel *N2*-arylated pyrano[2,3-*c*]pyrazol-6-ones **2** can be prepared in a selective manner by generating the anion of **1 (R=H)** with lithium hexamethyldisilazide in DMF and quenching with activated aryl halides. Sterically demanding groups such as phenyl as in **5** reduce reactivity significantly while electron-withdrawing substituents such as trifluoromethyl and phenyl at C4 of the pyranone ring as in **10** and **15** render the pyranone carbonyl particularly susceptible to attack by nucleophiles resulting in ring-opening to give novel crotonyl derivatives. Proof of structure required a variety of nmr methods involving proton, carbon, and nitrogen nuclei.

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INTRODUCTION

Since the early 1980s pyrano[2,3-*c*]pyrazoles **1** have been reported to possess a wide spectrum of biological activity of pharmaceutical interest [1]. We became interested in this fused ring system for potential agrichemical use as part of our discovery program. Although there are numerous examples of substitution at N1 of **1** [2], which are prepared using substituted hydrazines, there are few reports which discuss alkyl substitution at N2 [1a,1c,3] and the literature is silent on the synthesis and characterization of *N2*-arylated pyrano-[2,3-*c*]pyrazol-6-ones **2** which were of particular interest to us. Two studies featuring the *N*-alkylation of **1** indicate a preference for incorporation of the alkyl group at N2, but reaction is by no means selective with ratios of N2:N1 alkylation approximately 2:1 [1a,1c]. In contrast we have found that incorporation of an aryl group at N2 can be accomplished with much greater selectivity which has allowed access to novel *N2*-arylated pyrano[2,3-*c*]-pyrazoles **2**.

RESULTS AND DISCUSSION

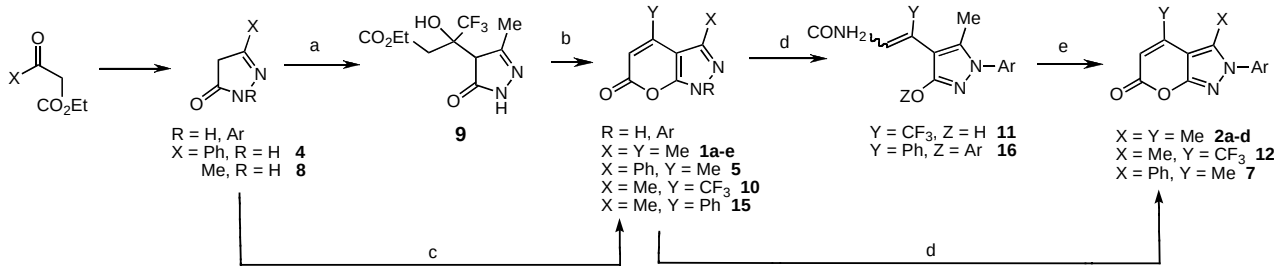
Treatment of a cold solution of **1a** in DMF with lithium hexamethyldisilazide in THF followed by an excess of 2-fluoro-5-trifluoromethylpyridine afforded a 59% yield of **2a** (Scheme 1) with no *N1*-arylated isomer isolated. The position of the pyridine ring at N2 of the pyrazole ring was established by a ^{1}H-^{15}N heteronuclear multiple bond correlation (HMBC) experiment which clearly indicated a correlation consistent with a three-bond coupling from the methyl protons at C3 of the pyrazole ring (3.01 ppm) to the nitrogen N2 at 205.1 ppm. The relative upfield chemical shift of this N2 nitrogen is consistent with the chemical shift of the substituted sp^3 nitrogen of pyrazoles [4].

These results were corroborated with those obtained from its regioisomer **1b** which was synthesized in an unequivocal manner from 5-trifluoromethyl-2-hydrazino-pyridine and ethyl acetoacetate. The ^{1}H-^{15}N HMBC spectrum of **1b** shows a correlation between the C3 methyl protons at 2.51 ppm with a nitrogen at 281.1 ppm consistent with an sp^2 nitrogen atom at N2 of the pyrazole ring.

The hexamethyldisilazide-generated anion of **1a** was also quenched with aryl halides to give *N2*-arylated pyrano[2,3-*c*]pyrazol-6-ones **2b**-**d** in moderate yields as the only isolated arylation products. Although use of additional aryl halide had minimal effect on product yield, the use of DMF as co-solvent had resulted in enhanced yields relative to THF alone in initial experiments.

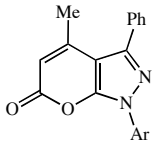
We next turned our attention to the *N*-arylation of **5** in which C3 is now occupied by the more sterically-demanding phenyl ring (Scheme 1). Pyrano[2,3-*c*]-pyrazol-6-one **5** was prepared from **4** [5] by the method of Khan and coworkers [2]. Due to the greater steric demand of the phenyl group at C3 and its electron-withdrawing nature, *N*-arylation proceeded in very low yield (10%) with 80% of the starting material recovered. The ratio of **7**:**6** was found to be 4:1. Assignment of the structures of **6** and **7** could not be done from ^{1}H-^{15}N HMBC experiments due to the absence of protons on the substituent at C3 which correlate to the nitrogen N2. Experiments designed to observe a nuclear Overhaeuser effect (nOe) between the *ortho*-phenyl protons and H5 of the pyridine ring of

Scheme 1: Synthesis of *N*-arylayted Pyrano[2,3-*c*]pyrazoles



a) $CF_3COCH_2CO_2Et$, 170 °C/2.5h (81%), b) 180 °C/2h (65% from **8**), c) ref. 2 (X = Ph), d) LHMDS, aryl halide, DMF/THF, e) 175 °C (Y = CF_3)

both structures were unsuccessful. Assignment of structure **6** was based on the substantial downfield shifts of the pyridyl and *otho* phenyl protons in the ^{1}H NMR spectrum of **6** versus those observed for **7**. Downfield shifts of this type have been found to be indicative of the degree of interannular conjugation and dihedral angles between the aromatic rings in phenyl substituted pyrazoles [6]. Steric interactions between the pyridinyl protons at N-2 and the *ortho* phenyl protons at C3 of the pyrazole ring impede coplanarity in **7** resulting in a larger dihedral angle between the rings, reduced interannular conjugation, and relative upfield shifts of the pyridinyl and ortho-phenyl protons.



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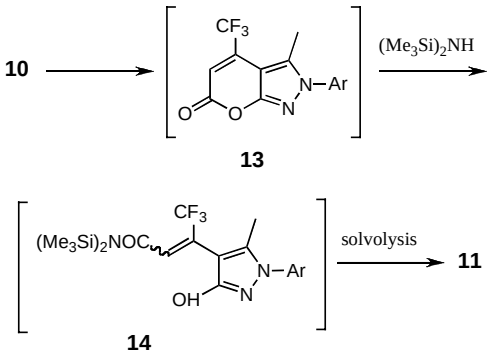
Unexpected results were obtained from the *N*-arylation of **10** in which a trifluoromethyl group is now at C4 (Scheme 1). Pyranopyrazole **10** was prepared by treatment of commercially available 5-methylpyrazol-3-one **8** with ethyl trifluoroacetate. The initially formed carbinol **9** is quite stable at 170 °C and was isolated and fully characterized but will undergo cyclization to **10** when heated slightly above its melting point. When the anion of **10** is treated with an excess of the aryl halide, *N*-arylation takes place at N2, however, the pyranone ring is also opened giving the primary amide **11** as the major product. The proton NMR spectrum for **11** showed three broad exchangeable singlets at 9.6, 7.2, and 6.8 ppm, while in the carbon NMR spectrum, there were two downfield signals not attributable to the pyridine. An HMBC spectrum indicated a long-range 4-bond cross-peak to the signal at 160 ppm, while the olefinic singlet at 7.0 ppm was the only proton signal that showed correlation to the other signal at 165 ppm - suggesting a carbonyl from an acid or amide group. A ^{1}H-^{15}N-HMBC experiment determined that the two proton signals at 7.2 and 6.8 were attached to a single nitrogen atom, confirming the presence of a primary amide group. This was confirmed by IR which showed an amide stretch at 1682 cm^{-1} and by mass spectral analysis which gave a molecular ion 17 amu above that of **12** consistent with addition of ammonia to **12**. It was found that heating **11** slightly above its melting point resulted in cyclization to **12**.

It is believed that **13** (Scheme 2) is initially formed but the electron-withdrawing capacity of the trifluoromethyl group at C4 enhances the electrophilicity of pyranone carbonyl carbon rendering it susceptible to attack by hexamethyldisilylamine to afford **14**. Solvolysis of the disilylamide then yields the observed primary amide **11**.

Pyranone ring opening was also observed when the 4-phenylpyranopyrazole **15** was arylated under these conditions affording the primary amide **16**. The reasons cited above for the ring opening of **13** apply here, but in this case the ring-opened hydroxypyrazole was also *O*-arylated.

Scheme 2



Although pyranone ring-opening had not been observed during the arylations of **1a** described above, we were prompted to examine the behavior of the 4-methyl derivatives **1c**-**d** and **2c** toward other nucleophiles. Conditions used were 1) sodium hydroxide (one equivalent) in methanol at room temperature and 2) excess 40% aqueous dimethylamine in THF at room

temperature. The results shown in Scheme 3 and Table 1 illustrate the ease with which the pyranone ring is opened under mild conditions to afford methyl esters **17a-b** and *N,N*-dimethylamides **18a-b** and **19** in moderate to good yields.

Scheme 3: Reaction of pyranones with nucleophiles.

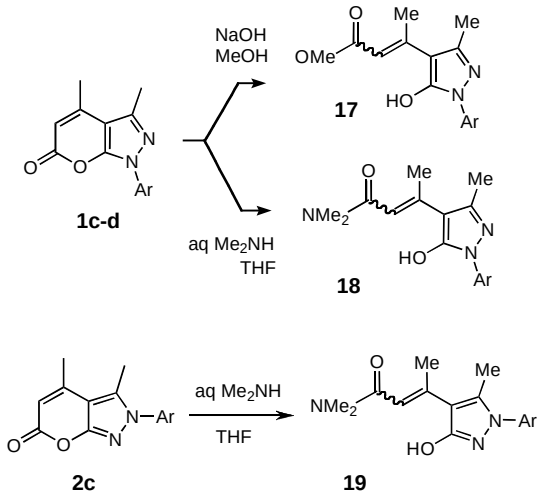


Table 1

Results from scheme 3

Compound	Ar	Yield %
17a	2-pyridyl	31
17b	*p*-Chlorophenyl	Quant
18b	*p*-Chlorophenyl	87
19c	6-CF_3-2-pyrimidinyl	70

CONCLUSIONS

Novel *N*2-arylated pyrano[2,3-*c*]pyrazol-6-ones **2** can be prepared in a selective manner by generating the anion of **1** with lithium hexamethyldisilazide in DMF and quenching with activated aryl halides.

Sterically-demanding groups such as phenyl as in **5** reduce selectivity somewhat while electron-withdrawing substituents such as trifluoromethyl and phenyl at C4 of the pyranone ring as in **10** and **15** render the pyranone carbonyl particularly susceptible to attack by nucleophiles resulting in ring-opening to give novel crotonyl derivatives. Proof of structure required a variety of nmr methods involving proton, carbon, and nitrogen nuclei.

EXPERIMENTAL

Melting points were obtained on a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected. Chromatography was performed on silica gel (230-400 mesh ASTM) obtained from EM Science, Darmstadt, Germany. Starting materials and reagents which were obtained from commercial sources were used without further purification. Proton, carbon-13 and nitrogen-15 NMR spectra were obtained on Bruker UltaShield 600 MHz, Bruker 400 MHz, or Varian Gemini 300 MHz spectrometers and are reported in parts per million (δ) downfield from tetramethylsilane or aqueous ammonia as internal reference. Mass spectra were obtained using an LC/MS system consisting of a Waters SunFire C18 5μ 4.6x50 mm column, Waters 2996 photodiode array and Alltech 2420 ELSD detectors, and a Waters Micromass ZQ mass spectrometer. Infrared spectra were obtained on a Digilab FTS 40 Pro spectrophotomer. Elemental analyses were provided by Midwest Microlabs of Indianapolis, IN.

General procedure for the preparation of pyrazol-6-ones 1b-1e. A 1-2 *M* solution of the hydrazine in ethyl acetoacetate was heated under reflux for two to four hours in a round-bottomed flask fitted with a Dean-Stark trap. Upon cooling the precipitated pyrazolone was collected.

3,4-Dimethyl-1-(5-trifluoromethyl-pyridin-2-yl)-1*H*-pyrano-[2,3-*c*]pyrazol-6-one (1b). Obtained using 2-hydrazino-5-trifluoromethylpyridine. Yield: 1.775 g (51%), tan solid, mp 214.5-216.5 °C; ^{1}H nmr δ (dimethyl sulfoxide-d_6) 9.00 (m, 1H), 8.41 (dd, 1H, *J* = 8.9 Hz and *J* = 2.3 Hz), 8.00 (d, 1H, *J* = 8.6 Hz), 6.03 (q, 1H, *J* = 1.3 Hz), 2.50 (s, 3H), 2.45 (d, 3H, *J* = 1.3 Hz); ms (API-ES+) m/z 310 ([M+H$^+$]$^+$, 100). A portion was recrystallized from ethyl acetate giving the following microanalytical data: *Anal*. Calcd. for $C_{14}H_{10}F_3N_3O_2$: C, 54.37; H, 3.26; N, 13.59. Found: C, 54.14; H, 3.20; N, 13.43.

1-(4-Chloro-phenyl)-3,4-dimethyl-1*H*-pyrano[2,3-*c*]pyrazol-6-one (1c). Obtained using 4-chlorophenylhydrazine. Yield: 2.68 g (58%), tan powder, mp 176-9 °C; ^{1}H nmr δ (dimethyl sulfoxide-d_6) 7.83 (d, 2H, *J* = 9.1 Hz), 7.65 (d, 2H, *J* = 9.1 Hz), 5.97 (q, 1H, *J* = 1.4 Hz), 2.48 (s, 3H), 2.45 (d, 3H, *J* = 1.1 Hz); ms (API-ES+) m/z 277 ([M+2+H$^+$]$^+$, 32), 275 ([M+H$^+$]$^+$, 100). *Anal*. Calcd. for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.20. Found: C, 61.22; H, 4.04; N, 10.08.

3,4-Dimethyl-1-pyridin-2-yl-1*H*-pyrano[2,3-*c*]pyrazol-6-one (1d). Obtained using 2-hydrazino-pyridine. Yield: 2.84 g (64%), pink solid, mp 229-233.5 °C; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 8.56 (m, 1H), 8.03 (m, 1H), 7.89 (m, 1H), 7.42 (m, 1H), 5.97 (d, 1H, *J* = 1.3 Hz), 2.48 (s, 3H), 2.44 (d, 3H, *J* = 1.3 Hz); ^{13}C nmr δ ($CDCl_3$) 160.0, 153.4, 151.3, 149.9, 149.5, 145.7, 139.1, 122.7, 115.3, 106.4, 103.3, 20.2, 15.3; ms (API-ES+) m/z 242 ([M+H$^+$]$^+$, 100). *Anal*. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.79; H, 4.46; N, 17.22.

3,4-Dimethyl-1-(4-trifluoromethyl-phenyl)-1*H*-pyrano[2,3-*c*]pyrazol-6-one (1e). Obtained using 4-trifluoromethylphenyl-hydrazine. Yield: 630 mg (38%), off-white powder, mp 152-4 °C; ^{1}H nmr δ (dimethyl sulfoxide-d_6) 8.03 (d, 2H, *J* = 8.9 Hz), 7.94 (d, 2H, *J* = 8.6 Hz), 5.99 (q, 1H, *J* = 1.0 Hz), 2.48 (s, 3H), 2.44 (d, 3H, *J* = 1.0 Hz); MS (API-ES+) m/z 309 ([M+H$^+$]$^+$, 100). A portion was recrystallized from ethyl acetate giving the following microanalytical data: *Anal*. Calcd. for $C_{15}H_{11}F_3N_2O_2$: C, 58.44; H, 3.60; N, 9.10. Found: C, 57.92; H, 3.59; N, 8.86.

General procedure for the preparation of pyrazolones 2a-2d. To a mixture cooled in a dry ice-isopropanol bath of 1 mmol of **1a** (R = H) in 0.5-1.0 mL of dimethylformamide was added dropwise *via* syringe 1.0 mmol of a 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran. After 30-90 minutes a solution of 2.6-3.0 equivalents of aryl halide in 0.5-1.0 mL in dimethylformamide was added dropwise *via* syringe. After stirring overnight at room temperature, the mixture was

concentrated to a residue which was partitioned between saturated sodium carbonate and dichloromethane. The layers were separated, the aqueous phase was extracted once with dichloromethane and the combined extracts were dried ($MgSO_4$). Concentration gave crude material which was purified by trituration, recrystallization, or chromatography.

3,4-Dimethyl-2-(5-trifluoromethyl-pyridin-2-yl)-2*H*-pyrano-[2,3-*c*]pyrazol-6-one (2a). Obtained using 2-fluoro-5-trifluoromethylpyridine. Chromatography on silica gel using 1:1 hexanes/ethyl acetate as eluant: Yield 186 mg (59%), mp 198-201 °C; ^{1}H nmr δ (deuteriochloroform) 8.75 (m, 1H), 8.11 (m, 2H), 5.97 (q, 1H, *J* = 1.1 Hz), 3.03 (s, 3H), 2.49 (d, 3H, *J* = 1.4 Hz); ms (API-ES+) m/z 310 ([M+H$^+$]$^+$, 100). *Anal.* Calcd. for $C_{14}H_{10}F_3N_3O_2$: C, 54.37; H, 3.26; N, 13.59. Found: C, 54.42; H, 3.37; N, 13.51.

3,4-Dimethyl-2-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-2*H*-pyrano[2,3-*c*]pyrazol-6-one (2b). Obtained using 2-chloro-5-trifluoromethyl-1,3,4-thiadiazole. Chromatography on silica gel using 1:1 hexanes/ethyl acetate as eluant to afford 86 mg (27%), mp 169-72 °C; ^{1}H nmr δ (deuteriochloroform) 6.05 (q, 1H, *J* = 1.4 Hz), 3.12 (s, 3H), 2.50 (d, 3H, *J* = 1.4 Hz); ms (70 eV, electron impact) m/z 316 (M$^+$, 100). *Anal.* Calcd. for $C_{11}H_7F_3N_4O_2S$: C, 41.77; H, 2.23; N, 17.72. Found: C, 41.55; H, 2.17; N, 17.35.

3,4-Dimethyl-2-(4-trifluoromethyl-pyrimidin-2-yl)-2*H*-pyrano[2,3-*c*]pyrazol-6-one (2c). Obtained using 2-chloro-4-trifluoromethylpyrimidine. Recrystallized from ethyl acetate: 190 mg (61%) of the titled compound, mp 193-5 °C; ^{1}H nmr δ (deuteriochloroform) 9.13 (d, 1H, *J* = 5.0 Hz), 7.60 (d, 1H, *J* = 4.9 Hz), 6.00 (q, 1H, *J* = 1.3 Hz), 3.00 (s, 3H), 2.48 (d, 3H, *J* = 1.3 Hz); ms (70 eV, electron impact) m/z 310 (M$^+$, 100). *Anal.* Calcd. for $C_{13}H_9F_3N_4O_2$: C, 50.33; H, 3.25; N, 18.06. Found: C, 50.20; H, 2.96; N, 17.58.

3,4-Dimethyl-2-(4-nitro-3-trifluoromethyl-phenyl)-2*H*-pyrano[2,3-*c*]pyrazol-6-one (2d). Obtained using 4-nitro-3-(trifluoromethyl)fluorobenzene. Trituration under diethyl ether: 161 mg (46%), mp 195-200 °C; ^{1}H nmr δ (dimethyl sulfoxide-d_6) 8.40 (d, 1H, *J* = 8.6 Hz), 8.17-8.23 (m, 2H), 6.07 (q, 1H, *J* = 1.4 Hz), 2.68 (s, 3H), 2.47 (d, 3H, *J* = 1.4 Hz); ms (API-ES-) m/z 352 ([M-H$^+$]$^+$, 100). *Anal.* Calcd. for $C_{15}H_{10}F_3N_3O_4$: C, 51.00; H, 2.85; N, 11.89. Found: C, 50.78; H, 2.88; N, 11.57.

4-Methyl-3-phenyl-1-(5-trifluoromethyl-pyridin-2-yl)-1*H*-pyrano[2,3-*c*]pyrazol-6-one (6) and **4-Methyl-3-phenyl-2-(5-trifluoromethyl-pyridin-2-yl)-2*H*-pyrano[2,3-*c*]pyrazol-6-one (7).** To a solution of 226 mg (1.00 mmol) of **5** (R = H) in 1.0 mL of dry DMF cooled in a dry ice/isopropanol bath was added dropwise *via* syringe 1.0 mL of 1.0 *M* lithium hexa-methyl-disilazide in THF. After 45 min a solution of 500 mg (3.03 mmol) of 2-fluoro-5-trifluoromethylpyridine in 0.5 mL of DMF was added dropwise *via* syringe. The contents were allowed to gradually warm to room temperature and were stirred overnight. The THF was removed *in vacuo* and the resulting oil was treated with ice water and diethyl ether. The layers were separated and the aqueous phase was extracted once with diethyl ether. The combined extracts were dried ($MgSO_4$) and concentrated to give 204 mg which consisted of approximately 80% starting material as indicated by lc/ms. This material was chromatographed on silica gel using dichloromethane and 95:5 dichlorome-thane/ethyl acetate to elute the *N*-arylated isomers separately giving 31 mg (8%) of 7, mp 192-194.5 °C; ^{1}H nmr δ (deuteriochloroform) 8.32 (m, 1H), 7.99 (dd, 1H, *J* = 8.7 Hz and *J* = 2.5 Hz), 7.92 (d, 1H, *J* = 8.7 Hz), 7.50-7.35 (m, 5H), 5.96 (q, 1H, *J* = 1.4 Hz), 1.88 (d, 3H, *J* = 1.4 Hz), 1.55 (s, 3H); ms (API-ES+) m/z 372 ([M+H$^+$]$^+$, 100). *Anal.* Calcd. for $C_{19}H_{12}F_3N_3O_2$: C, 61.45; H, 3.26; N, 11.32. Found: C, 61.28; H, 3.01; N, 11.12.

Titled compound **6** was eluted first affording 8 mg (2%) of a solid, mp 170-4 °C; ^{1}H nmr δ (deuteriochloroform) 8.92 (m, 1H), 8.13 (m, 2H), 7.63-7.52 (m, 5H), 6.00 (q, 1H, *J* = 1.1 Hz), 2.20 (d, 3H, *J* = 1.4 Hz), 1.58 (s, 3H); ms (API-ES+) m/z 372 ([M+H$^+$]$^+$, 100).

4,4,4-Trifluoro-3-hydroxy-3-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-butyric acid ethyl ester (9). A mixture of 508 mg (5.18 mmol) of **8** and 2.81 g (15.3 mmol) of 3,3,3-trifluoroethylacetoacetate was heated at 170 °C for 2.5 h and was allowed to cool and stand overnight. The mixture was triturated under diethyl ether to afford 919 mg (63%) of **9** as a light pink solid; ir (potassium bromide) 3499, 3367, 2518, 1712 cm^{-1}; ^{1}H nmr δ (dimethyl sulfoxide-d_6) 11.45 (br s, 1H), 9.90 (br s, 1H), 6.40 (br s, 1H), 3.98 (q, 2H, *J* = 7.1 Hz), 3.37 (d, 1H, *J* = Hz), 2.83 (d, 1H, *J* = 15.7 Hz), 2.19 (s, 3H), 1.11 (t, 3H, *J* = 7.1 Hz); ms (API-ES+) m/z 283 ([M+H$^+$]$^+$, 100);. A portion was recrystallized from methanol to give an analytical sample, mp 171-4. *Anal.* Calcd. for $C_{10}H_{13}F_3N_2O_4$: C, 42.55; H, 4.64; N, 9.93. Found: C, 42.43; H, 4.64; N, 9.88.

3-Methyl-4-trifluoromethyl-1*H*-pyrano[2,3-*c*]pyrazol-6-one (10). A mixture of 483 mg (4.92 mmol) of **8** and 2.70 g (14.7 mmol) of 3,3,3-trifluoroethylacetoacetate was heated in an oil bath held at 180 °C for 2 h after all solids had disappeared. Upon cooling the mixture was triturated under diethyl ether to give 696 mg (65%) of a pink solid, mp 175-182 °C; ^{1}H nmr δ (deuteriochloroform) 11.2 (br s, 1H), 6.45 (s, 1H), 2.58 (s, 3H); ^{13}C nmr δ ($CDCl_3$) 160.2, 159.5, 138.9 (q, *J* = 36.3 Hz, *C*-CF_3), 137.5, 121.0 (q, *J* = 273.8 Hz, *C*F_3), 109.6 (q, *J* = 5.5 Hz, H*C*=*C*CF_3), 94.8, 11.6; ms (API-ES+) m/z 219 ([M+H$^+$]$^+$, 100). *Anal.* Calcd. for $C_8H_5F_3N_2O_2$: C, 44.04; H, 2.31; N, 12.84. Found: C, 43.92; H, 2.39; N, 12.74.

4,4,4-Trifluoro-3-[3-hydroxy-5-methyl-1-(5-trifluoromethyl-pyridin-2-yl)-1*H*-pyrazol-4-yl]-but-2-enoic acid amide (11) and **3-Methyl-4-trifluoromethyl-2-(5-trifluoro–methyl-pyridin-2-yl)-2*H*-pyrano[2,3-*c*]pyrazol-6-one (12).** To a solution cooled in a dry ice/isopropanol bath of 218 mg (1.00 mmol) of **10** (R = H) in 1.0 mL of dry DMF was added dropwise *via* syringe 1.0 mL (1.00 mmol) of 1.0 *M* lithium hexamethyl–disilazide in THF. After 45 min a solution of 500 mg (3.03 mmol) of 2-fluoro-5-trifluoromethylpyridine in 1.0 mL of DMF was added dropwise. The solution was allowed to warm to room temperature and was stirred overnight. The solution was concentrated *in vacuo* and the residue was partitioned between diethyl ether and saturated sodium bicarbonate. The layers were separated, the aqueous phase was extracted once with chloroform and the combined organics were dried ($MgSO_4$). Concentration gave 161 mg consisting predominately of DMF. This material was treated with 1 mL of chloroform causing precipitation of a white solid. The mixture was chilled in ice and the solid was collected affording 46 mg of the amide **11**, mp 169-72 °C; ir (potassium bromide) 3409, 3187, 1682 cm^{-1}; ^{1}H nmr δ (dimethyl sulfoxide-d_6) 10.85 (br s, 1H), 8.78 (m, 1H), 8.29 (m, 1H), 7.86 (d, 1H, *J* = 8.6 Hz), 7.72 (br s, 1H), 7.38 (br s, 1H), 6.92 (m, 1H), 2.47 (s, 3H); ms (API-ES-) m/z 379 ([M-H$^+$]$^+$, 100); *Anal.* Calcd. for $C_{14}H_{10}F_6N_4O_2$: C, 44.22; H, 2.65; N, 14.73. Found: C, 44.28; H, 2.78; N, 14.56.

Compound **11** was heated at 170-5 °C for 15min and was allowed to cool forming **12** as a white solid, mp 156-9 °C; ^{1}H nmr δ (deuteriochloroform) 8.77 (m, 1H), 8.13 (dd, 1H, *J* = 8.9 Hz and *J* = 2.3 Hz), 8.07 (d, 1H, *J* = 8.6 Hz), 6.54 (s, 1H), 2.93

(s, 3H); ms (API-ES+) m/z 364 ([M+H$^+$]$^+$, 100). *Anal. Calcd.* for $C_{14}H_7F_6N_3O_2$: C, 46.29; H, 1.94; N, 11.57. Found: C, 46.18; H, 2.00; N, 11.51.

3-[5-Methyl-1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-3-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yloxy)-1*H*-pyrazol-4-yl]-3-phenyl-acrylamide (16). To a solution of 116 mg (0.513 mmol) of **15** (R = H) in 0.8 mL of dry DMF cooled in a dry ice/isopropanol bath was added dropwise 0.500 mL (0.500 mmol) of 1.0 *M* lithium hexamethyldisilazide in THF. After 30 min a solution of 188 mg (1.00 mmol) of the 2-chloro-5-trifluoromethyl-1,3,4-thiadiazole [7] in 0.5 mL of DMF was added dropwise *via* syringe. The contents were stirred overnight at room temperature. The volatiles were removed *in vacuo*, the residue was partitioned between diethyl ether and saturated sodium bicarbonate and the layers were separated. The aqueous phase was extracted once with diethyl ether and the combined organics were dried ($MgSO_4$). Concentration gave 224 mg which was chromatographed on silica gel to give 47 mg (17%) of **16**; ^{1}H nmr δ deuteriochloroform) 7.59-7.34 (m, 5H), 6.90 (s, 1H), 5.88 (br s, 1H), 5.36 (br s, 1H), 2.53 (s, 3H); ms (API-ES+) m/z 548 ([M+H$^+$]$^+$, 100). *Anal*. Calcd. for $C_{19}H_{11}F_6N_7O_2S_2$: C, 41.68; H, 2.03; N, 17.91. Found: C, 41.95; H, 2.07; N, 17.42.

3-(5-Hydroxy-3-methyl-1-pyridin-2-yl-1*H*-pyrazol-4-yl)-but-2-enoic acid methyl ester (17a). To a mixture of 121 mg (0.501 mmol) of **1d** in 3 mL of methanol was added 1.0 mL (1.0 mmol) of 1.0 *N* sodium hydroxide. After stirring at room temperature for one hour, tlc indicated no starting material remaining. Hydrochloric acid (1.0N, 1.00 mmol) was added and the methanol was removed *in vacuo*. The residue was extracted two times with diethyl ether, the combined extracts were washed with brine and were dried ($MgSO_4$). Concentration gave a material which was chromatographed by reverse-phase (C_{18} amide linker-modified) using gradient elution (0.1% acetic acid in 60:40 water/acetonitrile to 100% acetonitrile) to give 65 mg (47%) of the titled compound, mp 91-5 °C; ir (potassium bromide) 3433 (br), 1705 cm^{-1}; ^{1}H nmr δ (deuterio-chloroform) 13.5 (br s, 1H), 8.26 (m,1H), 7.89 (m, 2H), 7.19 (m, 1H), 6.02 (q, 1H, *J* = 1.3 Hz), 3.73 (s, 3H), 2.59 (d, 3H, *J* = 1.3 Hz), 2.38 (s, 3H); MS (API-ES-) 272 ([M-H$^+$]$^+$, 100);. A portion was recrystallized from diethyl ether/ethyl acetate to give the analytical sample, mp 97-98.5 °C. *Anal.* Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.52; H, 5.53; N, 15.38. Found: C, 61.27; H, 5.35; N, 15.16.

3-[3-Hydroxy-5-methyl-1-(4-trifluoromethyl-pyrimidin-2-yl)-1*H*-pyrazol-4-yl]-but-2-enoic acid dimethylamide (19c). To a mixture of 94 mg (0.303 mmol) of **2c** in 1.0 mL of THF was added 136 mg (1.21 mmol) of 40% aqueous dimethylamine. After 2 h at room temperature tlc indicated no starting material remaining. The solution was treated with 1.21 mL of 1.0 *N* hydrochloric acid causing precipitation of a white solid which was collected and dried *in vacuo* to give 75 mg (70%) of the titled compound; ^{1}H nmr δ (deuteriochloroform) 8.93 (d, 1H, *J* = 5.0 Hz), 7.36 (d, 1H, *J* = 4.9 Hz), 6.21 (br s, 1H), 2.90 (s, 3H), 2.61 (s, 3H), 2.14 (d, 3H, *J* = 1.6 Hz); ms (API-ES-) m/z 354 ([M-H$^+$]$^+$, 100). A portion was recrystallized from chloroform/ hexanes to give the analytical sample, mp 178 °C (dec). *Anal.* Calcd. for $C_{15}H_{16}F_3N_5O_2$: C, 50.70; H, 4.54; N, 19.71. Found: C, 50.87; H, 4.53; N, 19.17.

3-[1-(4-Chloro-phenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-(4)-ylidene]-*N*,*N*-dimethyl-butyramide (18b). To a mixture cooled in an ice bath of 1.00 g (3.64 mmol) of **1c** in 5 mL of THF was added dropwise 1.64 g (14.6 mmol) of 40% aqueous dimethylamine. The contents were allowed to warm to room temperature. After 3 h no starting remained (tlc). The solution was then treated with 1.0 *N* hydrochloric acid (approximately 10 mL) to give a Ph of 3-4. The mixture was diluted to 40 mL with water, was chilled in ice, and the solid was collected and vacuum dried to give 1.01 g (87%) of the titled compound; ir (potassium bromide) 1679 (s), 1649 (s) cm^{-1}; ^{1}H nmr δ (deuteriochloroform) pyrazolone tautomer 7.85 (d, 2H, *J* = 8.9 Hz), 7.33 (d, 2H, *J* = 8.9 Hz), 4.23 (s, 2H), 3.12 (s, 3H), 2.97 (s, 3H), 2.46 (s, 3H), 2.44 (s, 3H); ms (API-ES-) ms 320 ([M+2-H$^+$]$^+$, 30), 318 ([M-H$^+$]$^+$, 100);. A portion was recrystallized from hexanes/ethyl acetate to give the analytical sample, mp 130-1 °C. *Anal*. Calcd. for $C_{16}H_{18}ClN_3O_2$: C, 60.09; H, 5.67; N, 13.14. Found: C, 59.93; H, 5.56; N, 12.98.

3-[1-(4-Chloro-phenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-(4)-ylidene]-butyric acid methyl ester (17b). To a mixture cooled in ice of 1.0 g (3.64 mmol) of **1c** in 22 mL of methanol was added dropwise 7.4 mL (14.8 mmol) of 2.0 *N* sodium hydroxide. The contents were stirred at room temperature overnight, were cooled, and were treated with 7.4 mL of 2.0 *N* hydrochloric acid to give pH 4. The mixture was concentrated *in vacuo* to remove most of the methanol and was then diluted with water and extracted two times with diethyl ether. The combined extracts were dried ($MgSO_4$). Concentration gave 1.15 g (quantitative); ^{1}H nmr δ ($CDCl_3$) pyrazolone tautomer 7.90 (d, 2H, *J* = 8.9 Hz), 7.33 (d, 2H, *J* = 8.9 Hz), 4.19 (s, 2H), 3.74 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H); ms (API-ES-) m/z 307 ([M+2-H$^+$]$^+$, 36), 305 ([M-H$^+$]$^+$, 100). A portion was recrystallized from ethyl acetate to give the analytical sample, mp 121-123.5 °C. *Anal*. Calcd. for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.80; H, 5.01; N, 9.14.

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