New Regional Isomers of 1-Methyl-5-(trifluoromethyl)pyrazoles

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Utilizing the recently reported compound, 1-methyl-5-(trifluoromethyl)-2,3,4,5-tetrahydropyrazol-3-one, **4**, a series of regional isomers of 1-methyl-5-(trifluoromethyl)-3-chloropyrazole, newly substituted in the 4-position were prepared by original syntheses. Chief among them was the new regional 4-hydroxy isomer, **3a**, a linkage reagent valuable for preparing new SAR candidates in the bio-active pyrazole phenyl ether series.

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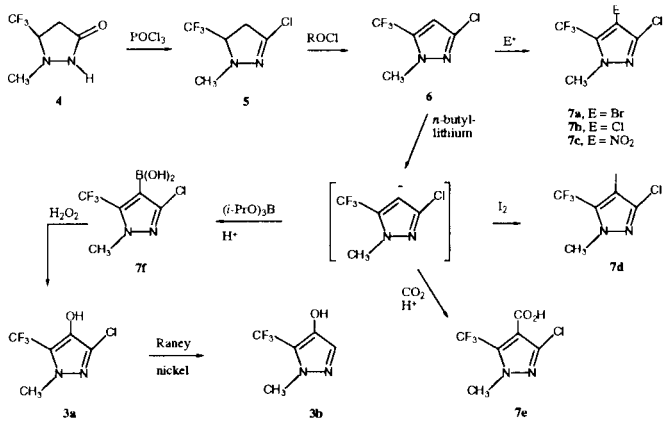
Recent articles [1-2] described the preparation of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-ol, **1**, and the isomeric 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-ol, **2**. The former material, particularly when chlorinated at the 4-position, has found utility in certain pyrazole phenyl ether herbicides [3]. It was consequently of interest to pursue new regional isomers of these pyrazoles for SAR studies, as applied to the phenyl ethers and related materials. As described in this note, in the course of preparing the new pyrazole linking agent, 3-chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-ol, **3a**, a number of other related materials were also synthesized for the first time.

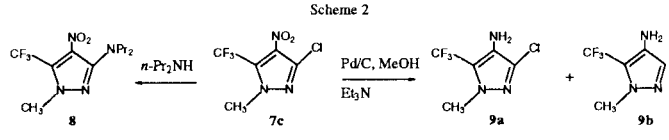
Starting material in this chemistry was **4**, [1]. As shown in Scheme 1, reaction of this material with phosphorus oxychloride gave an acceptable yield of **5**. Easy quantitative oxidation with positive halogen such as *t*-butyl hypochlorite or Chlorox™ gave **6**. This material is indeed a useful intermediate, since it undergoes substitution at the **4** position directly with strong electrophiles to give **7a-7c**, or as an easily formed, and well behaved carbanion with weaker electrophiles to give **7d,e** and **f**. The target compound **3a** is then produced from the novel pyrazole boronic acid **7f** by hydrogen peroxide oxidation. Hydrodechlorination then gives **3b**.

New amine derivatives are produced from **7c**, as shown in Scheme 2. This latter material possesses a sufficiently activated halogen to effect replacement by nucleophilic amine to give **8**. Alternatively, reduction of the nitro group gives **9a,b**. Finally, **7d** and **7f** can be used in transition metal catalyzed coupling reactions as shown in Scheme 3, wherein either a pyrazole iodide or pyrazole boronic acid couples respectively with an aryl boronic acid, or aryl iodide to give **10a** and **10b**.

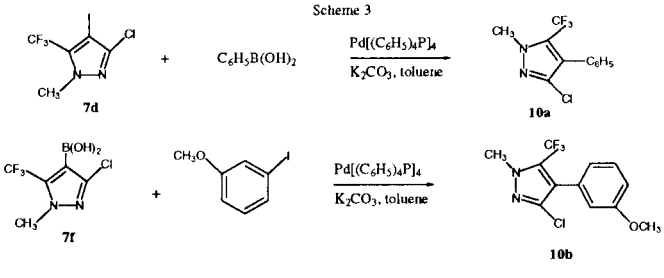
Scheme 1



Scheme 2



Scheme 3



EXPERIMENTAL

Melting points were determined on a Mel Temp ™ apparatus and are uncorrected. The ^1H and ^{19}F nmr spectra were recorded on an XL 360 (360 MHz) with the instrument referenced internally. Mass spectra (ms) were measured by either direct probe in the c.i. or e.i. mode, or by gcms (e.i.). Parent molecular ion (m/z) is expressed in all cases as molecular weight. Unless otherwise noted, boiling and sublimation points are recorded as oven temperatures during bulb-to-bulb (Kugelrohr) distillations. All microanalyses were performed by Atlantic Microlab Inc., P.O. Box 2288, Norcross, Georgia 30091.

3-Chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-ol (**3a**).

Crude **7f** (see below), (4 g, estimated to contain *ca* 3 g of **7f**, 13 mmoles) was placed in 20 ml of ether with 5 ml of acetic acid, then 4.5 ml of 30% hydrogen peroxide in 4.5 ml of water

was added [4]. There was no exotherm. The mixture was stirred 0.5 hour at 28-30°, then heated to reflux (41°) for *ca* 3 hours. Gc and gcms showed 60-70% was converted to pyrazol-4-ol, with the remainder either as boronic acid, **7f** or 4-*H*-pyrazole, **6** (gc of **7f** gives the peak for **6**). The reaction mixture was permitted to stir over 2 days at room temperature, with gcms showing perhaps a slight improvement in yield. Layers were then separated, and the water layer extracted with ether. The combined ether layers were washed with ferrous ammonium sulfate, then dried over magnesium sulfate. The filtered and stripped solution gave 6 g of residue which contained acetic acid. The material was consequently dissolved in 5% sodium hydroxide, then extracted twice with ether. The aqueous base solution was then acidified with 37% hydrochloric acid to give an oil, which was extracted 3x with ether. The combined ether extracts were washed once with water, then dried over magnesium sulfate. The material was filtered, stripped, (1.9 g) and bulb-to-bulb distilled under high vacuum to give 1.43 g (54%), mp 66-68°, with 0.3 g of residue. In another preparation this procedure was scaled to 5x the above charges to give 6.7 g (50%) of product; ^{1}H nmr (deuteriochloroform): δ 3.97 (s, 3H, NCH_3), 5.02 (b, 1H, OH); ^{19}F nmr: δ -61.05 (s, CF_3); gcms/ei: m/z = 200 (1 Cl).

Anal. Calcd. for $C_5H_4ClF_3N_2O$: C, 29.95; H, 2.01; Cl, 17.68; N, 13.97. Found: C, 30.00; H, 1.98; Cl, 17.58; N, 14.00.

1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-ol (**3b**).

Material **3a** (2.0 g) was heated in ethanol with 20 g of fresh Raney nickel for several hours, until gc and gcms indicated that a substantial amount of hydrodechlorination had taken place. More Raney nickel was added as needed (25 g). The material was filtered, washed with large amounts of ethanol, and the filtrate carefully treated on the rotovap under water pump vacuum to 70°. The residue was bulb-to-bulb distilled, then the distillate obtained eluted with the Chromatotron™ with 15% ethyl acetate in cyclohexane, to give after recrystallization from methylcyclohexane, 170 mg (12%), mp 52-53°; ^{1}H nmr (deuteriochloroform): δ 3.82 (s [excluding long range coupling with CF_3], 3H, NCH_3), 6.3 (very b, 1H, OH), 7.08 (s, 1H, 3-pyrazol H); ^{19}F nmr: δ -60.35 (s [excluding long range coupling with CH_3], CF_3); gcms/ei: m/z = 166.

Anal. Calcd. for $C_5H_5F_3N_2O$: C, 36.16; H, 3.03; N, 16.87. Found: C, 35.90; H, 3.04; N, 16.59.

3-Chloro-4,5-dihydro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (**5**).

Compound **4** [1] (1.68 g, 10 mmoles) was placed in 10 ml of acetonitrile and 1.6 g of phosphorus oxychloride added. The mixture was refluxed for 40 minutes, when gc indicated all had reacted. The mixture was cooled, whereupon it became turbid, and was decanted from a sticky gum that adhered to the wall of the flask. The material was carefully stripped on the rotovap to 40° (water pump vacuum) to give 1.8 g of residue. This material was bulb-to-bulb distilled at 40-110° (100 mm) to give 1.0 g (54%) of clear colorless liquid as product. The residue weighed 0.8 g.

In another preparation, 10 mmoles of **4** reacted with 2 g of phosphorus oxychloride in methylene chloride with reflux for 4 hours, then treatment with water (not to exceed 30°). Rotovap treatment to 35° gave 1.74 g, which on bulb-to-bulb distillation at 100 mm vacuum gave 0.08 g of residue and 1.35 g of distillate (^{31}P and ^{1}H nmr indicated 4% methylene chloride by weight as the only impurity).

In still another preparation 30 mmoles of **4** was mixed with 20 ml of phosphorus oxychloride, and 4 g of potassium chloride, then heated at reflux for 0.5 hour. On cooling, 11 ml of phosphorus oxychloride was removed (atmospheric pressure) to a pot temperature of 120°, and the residue treated with 300 ml of ice water/10 ml of ethanol for 15 minutes at 15-18° to destroy the remaining phosphorus halide. The mixture was extracted with 50 ml of methylene chloride. The latter was carefully removed on the rotovap to 40-45° at 25 mm, then the remaining 4.3 g bulb-to-bulb distilled at 65-120° (100 mm) to give 4.0 g of colorless liquid as product (71%) and 0.2 g of residue.

In other preparations, *ca* 60-70% yields were obtained as given above, except potassium chloride was omitted. It was found that residual amounts of water in the product would slowly hydrolyze the material. This could be attenuated by storage in the refrigerator. Drying over magnesium sulfate also was helpful; ^{1}H nmr (deuteriochloroform): δ 2.83 (s, 3H, NCH_3), 3.07 (m's, 2 H, 4-CH_2), 3.57 (m, 1H, 5-CH); ^{19}F nmr: δ -75.5 (s [excluding vicinal ^{1}H coupling] CF_3); gcms/ei: m/z = 186 (1 Cl).

Anal. Calcd. for $C_5H_6ClF_3N_2$: C, 32.19; H, 3.24; Cl, 19.00; N, 15.02. Found: C, 32.37; H, 3.31; Cl, 18.80; N, 14.82.

3-Chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (**6**).

In 10 ml of benzene **5** (2.8 g, 15 mmoles) was dissolved and the solution cooled to 5-10° and 1.8 g of *t*-butyl hypochlorite in 5 ml of benzene was added dropwise, keeping the temperature below 10°. The flask was then set for distillation at atmospheric pressure through a small vigreux column. The product was collected at 130° with the pot temperature at 140° to give 2.0 g (72%), (forerun contained water, generated by reaction of *t*-butyl alcohol with hydrogen chloride). Very little residue was encountered. In another run, 5.6 g of starting material gave 4.3 g (77%) of product using Chlorox™ as the oxidizing agent; ^{1}H nmr (deuteriochloroform): δ 3.85 (s, 3H, NCH_3), 6.44 (s, 1 H, 4-CH); ^{19}F nmr: δ -62.67 (s [excluding small vicinal ^{1}H coupling], CF_3); gcms/ei: m/z = 184 (1 Cl).

Anal. Calcd. for $C_5H_4ClF_3N_2$: C, 32.54; H, 2.18; Cl, 19.21; N, 15.18. Found: C, 32.36; H, 2.21; Cl, 19.13; N, 15.09.

4-Bromo-3-chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (**7a**).

On the steam bath **6** (1 g, 5.4 mmoles), mixed with 1.5 g of bromine and 0.13 g of iron powder, was heated for 12 hours before gc indicated nearly complete reaction. The material was taken up in ether, and washed with sodium thiosulfate solution to remove excess bromine, then dried over magnesium sulfate, followed by rotary evaporation to 60° (25 mm). Bulb-to-bulb distillation of the residue at 25-50° (0.8 mm) gave 0.7 g (53%); ^{1}H nmr (deuteriochloroform): δ 3.89 (s, 3H, NCH_3); ^{19}F nmr: δ -61.64 (s, CF_3); gcms/ei: m/z = 262 (1 Br), (1 Cl).

Anal. Calcd. for $C_5H_3BrClF_3N_2$: C, 22.80; H, 1.15; N, 10.63. Found: C, 23.59; H, 1.31; N, 10.11.

3,4-Dichloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (**7b**).

Material **6** (0.9 g, 5 mmoles) was dissolved in acetonitrile, cooled to 0-5° and 1.0 g of dichlorodimethylhydantoin added, then the mixture allowed to warm to ambient temperature. The material was refluxed until appreciable chlorination had occurred. Purification proceeded by water washing, ether extraction, then distillation to remove solvent *and* starting material.

The residue was distilled to give a liquid product containing traces of solvent; gcms/ei: m/z = 218 (2 Cl).

3-Chloro-1-methyl-4-nitro-5-(trifluoromethyl)-1*H*-pyrazole (**7c**).

Material **6** (5 g, 27 mmoles) was added in increments to a mixture of 2 ml of 90% nitric acid in 25 ml of concentrated sulfuric acid. The temperature rose to 45°, then the remainder of the pyrazole was added fairly rapidly. The mixture was then heated to 85° for 1 hour. The material was poured into ice and filtered to give white solid. Gc showed only one peak. The material was air dried to give 94% yield with analytical sample obtained by recrystallization from methylcyclohexane. Air drying of the latter gave abnormal weight loss (2.0 g) due to facile tendency of this material to sublime, even at atmospheric pressure, mp 62-64°; ^{1}H nmr (deuteriochloroform): δ 4.08 (s, 3H, NCH_3); ^{19}F nmr: δ -59.85 (s, CF_3); gcms/ei: m/z = 229 (1 Cl).

Anal. Calcd. for $C_5H_3ClF_3N_3O_2$•0.3 H_2O: C, 25.56; H, 1.53; N, 17.88. Found: C, 25.47; H, 1.55; N, 17.77.

3-Chloro-4-iodo-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (**7d**).

Material **6** (5 g, 27 mmoles) was dissolved in 40 ml of dry tetrahydrofuran, cooled to -78° and 11 ml of 2.5 *M n*-butyllithium was added at that temperature dropwise. After addition, the mixture was stirred at the same temperature for 1 hour, then a solution of 6.9 g (27 mmoles) of iodine in tetrahydrofuran was added dropwise at -78°, with an additional 30 minutes stirring. The reaction mixture was then allowed to warm to -10° and 10 ml of 10% hydrochloric acid was added, and the mixture was allowed to stand two days. After ether addition and layer separation, the ether layer was washed once with sodium thiosulfate solution, wherein the color lightened to yellow. The ether layer was then washed once with water, and the combined water and thiosulfate solution washed again with fresh ether. The dried (magnesium sulfate) ether solution was stripped to give a solid residue that was bulb-to-bulb distilled with the product fraction collected after the oven temperature had reached 60°. The product, 6.9 g (82%) was collected between 60-90° (0.8 mm). Recrystallization was from cold (-78°) hexanes, mp 58-60°; ^{1}H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3); ^{19}F nmr: δ -60.65 (s, CF_3); gcms/ei: m/z = 310 (1 Cl).

Anal. Calcd. for $C_5H_3Cl\ F_3IN_2$: C, 19.35; H, 0.97; Cl, 11.42; I, 40.88; N, 9.02. Found: C, 19.45; H, 1.00; Cl, 11.33; I, 40.69; N, 8.90.

3-Chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic Acid (**7e**).

Material **6** (5 g, 27 mmoles) was dissolved in 40 ml of dry tetrahydrofuran with 3.3 g of N,N,N'N'-tetramethylethylene tetramine (TMEDA), cooled to -78°, then 21 ml of 1.3 *M sec*-butyllithium in cyclohexane added. The reaction mixture was permitted to stir *ca* 0.5 hour, then solid carbon dioxide added, and the reaction mixture permitted to warm to room temperature. Water was added, then acidified with 37% hydrochloric acid and with ether the whole transferred to a separatory funnel (1 liter) and more ether added with more water. The aqueous layer was extracted once more with fresh ether, then the combined ether layers washed with 3% hydrochloric acid, followed by a water wash. After drying over magnesium sulfate, the ether portion was filtered, stripped to 60° (30 mm) to give 6.1 g of solid. Recrystallization from methylcyclohexane gave 4.6 g (75%), mp 135-137°; ^{1}H nmr (deuteriochloroform): δ 4.16 (s, 3H, NCH_3); ^{19}F nmr: δ -59.54 (s, CF_3); dpms/ei: m/z = 228 (1 Cl).

Anal. Calcd. for $C_6H_4ClF_3N_2O_2$: C, 31.58; H, 1.77; Cl, 15.51; N, 12.28. Found: C, 31.75; H, 1.80; Cl, 15.68; N, 12.23.

[3-Chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]-boronic Acid (**7f**).

Material **6** (5 g, 27 mmoles) was dissolved in 40 ml of dry tetrahydrofuran and cooled to -78°, and 11 ml of 2.5 *M n*-butyllithium in hexanes added dropwise at this temperature. After stirring *ca* 1 hour, 5.5 g (8 ml) of triisopropyl borate was added at -78° over 0.5 hour. The reaction mixture was then allowed to warm to -20° and 20 ml of 10% hydrochloric acid added, followed by ether. The aqueous solution registered *p*H = 1 on water wash. A second water wash was performed, and then the ether layers dried over magnesium sulfate. After solvent removal on the rotovap a viscous brown oil was obtained (6.9 g) showing two isopropyl groups. The oil was recrystallized from water to give a white solid, mp 99-109°. The crude could be used effectively for oxidation and coupling reactions without further purification; ^{1}H nmr (deuteriochloroform): δ 3.92 (s, 3H, NCH_3), 5.12 (b, 2H, BOH); ^{19}F nmr: δ -59.35 (s, CF_3); dpms/ci: m/z = 228 and 242, 256.

Anal. Calcd. for $C_5H_5BClF_3N_2O_2$: C, 26.31; H, 2.21; Cl, 15.52; N, 12.27. Found: C, 26.10; H, 2.31; Cl, 15.52; N, 12.04.

1-Methyl-4-nitro-*N,N*-dipropyl-5-(trifluoromethyl)-1*H*-pyrazol-3-amine (**8**).

Compound **7c** (0.5 g, 2.2 mmoles) was mixed with 4 ml of di(*n*-propyl)amine (as solvent and reactant) and refluxed for 72 hours until appreciable product (by gc assay) had been formed. Bulb-to-bulb distillation gave 0.3 g (46%) at 70-110° (0.7 mm). This distillate was subjected to flash chromatography, with a yellow product band moving faster than the starting material (colorless band); ^{1}H nmr (deuteriochloroform): δ 0.8 (t, 6H, CH_2CH_3), 1.49 (m, 4H, CH_2CH_3), 3.09 (t, 4H, NCH_2), 3.85 (s, 3H, NCH_3); ^{19}F nmr: δ –60.00 (s, CF_3); gcms/ei: m/z = 294 .

Anal. Calcd. for $C_{11}H_{17}F_3N_4O_2$: C, 44.90; H, 5.82; N, 19.04. Found: C, 45.00; H, 5.87; N, 18.80.

3-Chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-amine (**9a**).

Compound **7c** (4.6 g, 20 mmoles) was charged into a hydrogenation bottle with 2.1 g of triethylamine in ethanol, with Pd/C catalyst. Hydrogenation gave a mixture of the title product and **9b** (see below). The reaction mixture was filtered through double filter paper, then stripped of alcohol to 45° (water pump). The thick slurry was treated with ether, after which filtration gave 2.1 g of triethylamine hydrochloride. The filtrate was evaporated (45° maximum) to give 3.3 g of crude material. Chromatotron™ treatment with 5% ethyl acetate in cyclohexane gave fraction 3 as title compound, 0.75 g (19%); this was bulb-to-bulb distilled at 80-130° (0.7 mm); ^{1}H nmr (deuteriochloroform): δ 3.38 (b, 2H, NH_2), 3.81 (s [excluding long range coupling with CF_3], 3H, NCH_3); ^{19}F nmr: δ -63.36 (s [excluding long range coupling with CH_3], CF_3); gcms/ei: m/z = 199 (1 Cl).

Anal. Calcd. for $C_5H_5ClF_3N_3$: C, 30.09; H, 2.53; Cl, 17.77. Found: C, 30.13; H, 2.62; Cl, 17.19.

1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-amine (**9b**).

The title compound was obtained as fraction 6 in the above preparation for **9a**. The yield was 0.8 g (24%), mp 38-40°; ^{1}H

nmr (deuteriochloroform): δ 3.32 (s, 2H, NH_2), 3.78 (s [excluding long range coupling with CF_3], 3H, NCH_3), 6.99 (s, 1H, 3-pyrazole H); ^{19}F nmr: δ -59.19 (s [excluding long range coupling with CH_3], CF_3); gcms/ei: m/z = 165 .

Anal. Calcd. for $C_5H_6F_3N_3$: C, 36.37; H, 3.66; N, 25.45. Found: C, 36.40; H, 3.64; N, 25.39.

3-Chloro-1-methyl-4-phenyl-5-(trifluoromethyl)-1*H*-pyrazole (**10a**).

Compound **7d** (1.55 g, 5 mmoles) was placed in 15 ml of toluene, 5 ml of 2 *M* potassium carbonate and 170 mg of $Pd[(C_6H_5)_3P]_4$ with 0.8 g of phenyl boronic acid in 2.5 ml of methanol was added. This mixture was refluxed 4 days with more toluene and more water added. Workup proceeded with an ether extraction, water wash, and magnesium sulfate drying. After filtering and stripping, bulb-to-bulb distillation followed by hexanes recrystallization gave 640 mg (49%), mp 32-33°; ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, NCH_3), 7.23-7.35 (m's, 5H, ArH); ^{19}F nmr: δ -59.02 (s, CF_3); gcms/ei: m/z = 260 (1 Cl).

Anal. Calcd. for $C_{11}H_8Cl\,F_3N_2$: C, 50.69; H, 3.09; Cl, 13.60; N, 10.75. Found: C, 50.64; H, 3.04; Cl, 13.68; N, 10.77.

3-Chloro-4-(3-methoxyphenyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (**10b**).

Compound **7f** (2.3 g, 10 mmoles) was placed in 20 ml of glyme with 2.5 g of 3-iodoanisole, 100 mg of fresh $Pd[P(C_6H_5)_3]_4$ and 6 ml of 2 *M* potassium carbonate. The material was heated at reflux. Gcms showed only partial reaction. Workup by the usual base and water washes, rotovap and bulb-to-bulb distillation gave 100 mg. This was eluted on a 2 mm thick Chromatotron™ plate to give 60 mg (2.1%) of pure material as an oil that eventually solidified; ^1H nmr (deuteriochloroform): δ 3.74 (s, 3H, OCH_3), 3.93 (s [excluding long range coupling with CF_3], 3H, NCH_3), 6.76-6.88 (m's, 3H, ArH), 7.22-7.27 (m, 1H, ArH); ^{19}F nmr: δ -59.34 (s, CF_3); gcms/ei: m/z = 290 (1 Cl).

Anal. Calcd. for $C_{12}H_{10}ClN_2F_3O$: C, 49.59; H, 3.47; N, 9.64. Found: C, 49.73; H, 3.44; N, 9.54.

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[4] Adapted from a procedure detailed for phenols in Organic Synthesis, Vol **V**, p 918.