Novel Perfluoroalkyl-Substituted Pyrazoles. 1. Hydroxypyrazoles

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Addition of methylhydrazine to a variety of haloalkyl-substituted α,β-unsaturated esters gives 1,5-disubstituted 3-hydroxypyrazoles, in contrast to the more common synthesis from β-ketoesters, which gives 1,3-disubstituted 5-hydroxypyrazoles. This reaction is used to prepare several novel pyrazoles bearing haloalkyl substituents. Criteria for assignment of structures have been developed based on physical and spectroscopic properties of the isomers. The regiochemical preference in this addition is considered on the basis of steric, electronic, and mechanistic factors.

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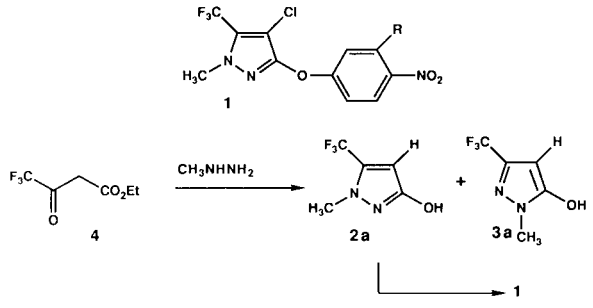
Introduction.

Pyrazole phenyl ether herbicides **1** [1] are a new class of diaryl ether herbicides with exceptionally high unit activity. In the course of investigating these herbicides, a substantial quantity of hydroxypyrazole **2a** [2,3], was required as an intermediate in the preparation of **1**. Existing technology [2] led to a mixture of hydroxypyrazoles **2a** and **3a** in which the desired isomer **2a** was a minor constituent (Scheme I), and thus research was initiated in an effort to improve the efficiency of the preparation of **2a**. We wish to report the successful outcome of this research effort [4,5].

Scheme I

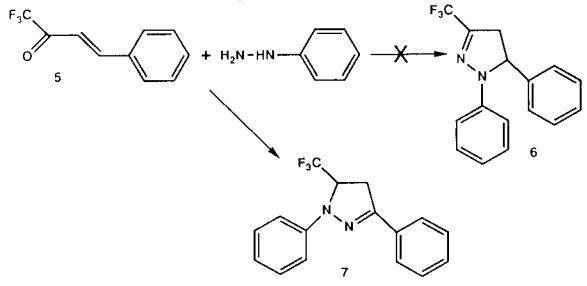


Results.

Synthesis from Crotonates.

Our initial approach was inspired by the first reaction in Scheme II, which had been observed previously in conjunction with other work. Addition of phenylhydrazine to enone **5** had been reported [6] to give the pyrazoline **6**, however upon repeating this work we found that the product was in fact the isomeric structure **7**. This structure was suggested by the pmr spectrum, which showed a pattern indicative of a CF_3-CH-CH_2C= structure, and the structure shown was confirmed by X-ray crystallography. It was apparent from the structure of the product that the more nucleophilic nitrogen of the arylhydrazine (in this case the unsubstituted nitrogen) had undergone 1,4-addition to the unsaturated ketone in **5**. If the more nucleophilic nitrogen of methylhydrazine (now the substituted nitrogen) would preferentially add to the β-carbon of a β-CF_3-substituted α,β-unsaturated ester the substitution pattern of the desired pyrazole **2a** would result [7]. The readily available trifluorocrotonate **8** [8] was chosen to test this hypothesis.

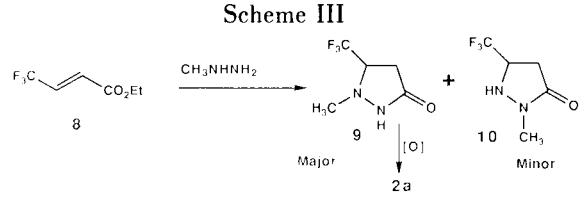
Scheme II



While the addition of hydrazines to α,β-unsaturated carbonyl compounds to form a five-membered heterocycle is well known, literature precedent does not clearly predict which isomer, or mode of addition of the substituted hydrazine, should predominate [9-11].

Trifluorocrotonate **8** reacted exothermically with methylhydrazine to give a 90:10 mixture of isomeric pyrazolines, and the major product was isolated in 71-88% yield after recrystallization (Scheme III). The structure of the major product was shown to be **9** by conversion to the desired hydroxypyrazole **2a**, and the isomeric minor product was thus assigned structrue **10**. This conversion was carried out using iron(III) chloride in refluxing ethanol, and although this method was successful in proving the structure of the intermediate adducts, yields were low and separation of the product from the iron(II) salts was tedious. Thus other routes to the desired product were investigated.

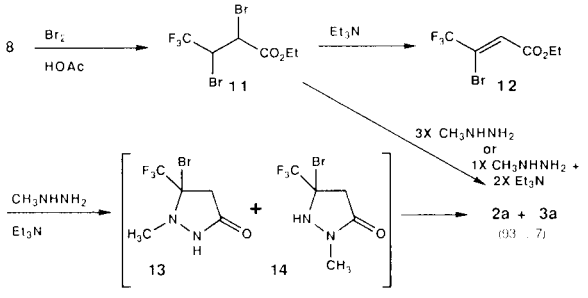
Scheme III



Synthesis from Halocrotonates.

With the regioselective synthesis of hydroxypyrazoles from unsaturated carbonyl compounds now established, alternatives to the troublesome oxidation step were investigated. These generally involved raising the oxidation state of the unsaturated ester substrate by incorporating a substituent on the double bond which would later undergo elimination to give the pyrazole oxidation state in the product [12-14]. The first of these proceeded *via* incorporation of a bromine substituent as shown in Scheme IV.

Scheme IV



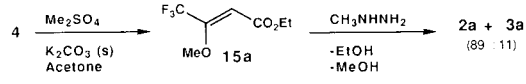
Crotonate **8** reacted slowly with excess bromine in refluxing acetic acid for 10 to 12 days and gave dibromide **11** [15]. This material underwent dehydrobromination readily to give bromide **12**, which reacted with methylhydrazine to give the addition products. The intermediate bromopyrazolines **13** and **14** were not observed. In the initial attempt with one equivalent of methylhydrazine an equimolar mixture of the pyrazoles **2a** and **3a**, and the starting bromocrotonate **12** was observed since the methylhydrazine was sufficiently basic to bring about elimination of hydrogen bromide from **13** and **14**. Treatment of this mixture with one equivalent of triethylamine brought about complete conversion to **2a** and **3a**. The same result could be attained by treating **12** with two equivalents of methylhydrazine, or **11** could simply be treated with three equivalents of methylhydrazine or with one equivalent of methylhydrazine and two equivalents of triethylamine. The hydroxypyrazoles **2a** and **3a** were formed in all cases in a ratio of 93:7, and the desired product **2a** could be isolated in up to 72% yield.

Synthesis from Enol Ethers.

While a viable laboratory route to **2a** was now apparently in hand, a number of difficulties remained. The bromo compounds **11** and **12** were potent lachrymators, and **8** was a rather expensive compound, being derived from ethyl trifluoroacetoacetate **4** by reduction and dehydration. Furthermore the slow reaction of **8** with bromine over 10 to 12 days was inconvenient. Finally, the idea of reducing **8** only to oxidize with bromine to **11** or **12** was aesthetically as well as economically displeasing. Thus attention was turned to yet another derivative of trifluorocrotonate, the enol ether **15a**. Literature precedent for pyrazole synthesis from this sort of substrate existed in the synthesis of diphenylpyrazolones from β-ethoxycinnamate and phenylhydrazine. This condensation was reported to give the isomer analogous to **2a**, namely 1,5-diphenylpyrazolin-3-one, although the presence of small amounts of the other isomer would almost certainly have escaped detection in 1906 [16]. A more recent report on the addition of arylhydrazines to ethoxymethylenemalonate indicated that the desired mode of initial Michael addition to a β-alkoxy-α,β-unsaturated ester could be achieved, albeit in the presence of alkoxide base [17]. A number of other related syntheses have been reported in the literature [9-11,17-21].

Synthesis of the desired enol ether **15a** directly from **4** had not been previously reported, but a literature method for preparing the corresponding ethoxy compound *via* a Wittig reaction of carboethoxytriphenylphosphorane and ethyl trifluoroacetate was known [22]. This reaction suffered from low yields and tedious workup, so an improved route to **15a** was sought as shown in Scheme V. Most literature reports on the alkylation of **4** [23] report competing C-alkylation, but a convenient procedure reported for the *O*-alkylation of ethyl acetoacetate [24] using dimethyl sulfate and solid potassium carbonate in acetone gave very good results with the fluorinated ketoester **4**. Enol ether **15a** was produced in distilled yields of 79% to 87%. Two complicating factors should be noted: The reaction required a 25% to 50% excess of dimethyl sulfate to force it to completion; without this excess the reaction would stop at about 60% conversion. Also, this excess dimethyl sulfate appeared in the crude product and resulted in a purification problem since its boiling point was only 9° above that of **15a** at the distillation pressure, thus requiring careful fractionation. (This was to become a more difficult problem later with higher boiling homologs of **15a**.) This problem was overcome by adding an amount of triethylamine equivalent to the excess dimethyl sulfate remaining prior to workup and partitioning the resulting ammonium salt into a small amount of water. Simple distillation then sufficed to purify **15a** with no reduction in yield.

Scheme V



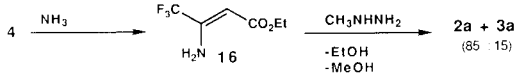
Enol ether **15a** reacted exothermically with methylhydrazine to give a mixture which contained a methoxypyrazolinone and two hydroxypyrazoles by pmr. Upon standing the pyrazoline was converted into hydroxypyrazole **2a**, and integration of the spectrum indicated that the regioisomeric ratio was 89:11 favoring the 3-hydroxypyrazole and its pyrazoline precursor. Recrystallization brought about completion of the elimination of methanol and gave

2a in 70% to 80% isolated yields.

Synthesis from Enamines.

Investigation of selective routes to hydroxypyrazoles such as **2a** was continued in an effort to eliminate the potential hazard associated with use of highly toxic dimethyl sulfate. The enamine **16** [25] was investigated as shown in Sheme VI. Some precedence for this reaction existed in the literature [26], but without a clear way of predicting the regiochemistry. Some other related reactions have been reported in the literature [27-37].

Scheme VI



The enamine derivative could be prepared very simply from ketoester **4** by passing gaseous ammonia through the neat liquid with heating. Reaction of enamine **16** with methylhydrazine proceeded smoothly at 50-60° with spontaneous elimination of ammonia to give an 85:15 mixture of **2a** and **3a**. Heating to higher temperatures gave a faster reaction but a less favorable isomer ratio.

Preparation of Novel Hydroxypyrazoles.

While the route to hydroxypyrazole **2a** from enamine **16** appeared to be the most efficient, the enol ether route proved to be important for the preparation of novel hydroxypyrazoles bearing other haloalkyl substituents. The C_2F_5 and CF_2Cl examples **2b** and **2c** were prepared by this route as shown in Table I along with product ratios and yields for the CF_3 example **2a** for comparison. The C_2F_5 example **2b** was initially synthesized from the dibromide *via* the route shown in Scheme IV, but bromination of the alkene was very slow and the yield of **2b** poor.

Attempts to prepare the CCl_3 substituted 3-hydroxypyrazole **2c** by this route were not successful. The enol ether was prepared, albeit in low yield, but no characterizable products could be isolated upon reaction with methylhydrazine. The gc-ms investigation of the reaction mixture revealed several peaks containing dichlorinated and monochlorinated products, thus indicating that the hydrazine had reacted with the CCl_3 group.

Finally, an attempt was made to prepare the 1,5-dimethyl substituted hydroxypyrazole **18** by reacting the enol ether **17** derived from ethyl acetoacetate with methylhydrazine (Scheme VII). The methyl enol ether **17a** [24] gave a complex mixture of products, while the trimethylsilyl enol ether **17b** gave only the 1,3-dimethyl substituted product **19**.

Scheme VII

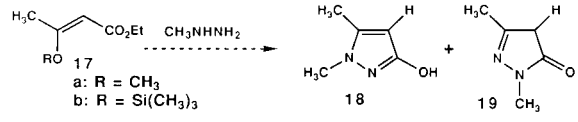
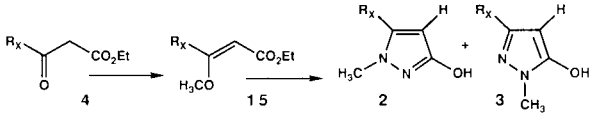


Table I. Synthesis of Haloalkyl Hydroxypyrazoles via Enol Ether Route (Scheme V)



Entry	R_X	% Yield 15	Ratio 2 : 3	% Yield 2
a	CF_3	87	89 : 11	70
b	C_2F_5	86	45 : 55	30
c	CF_2Cl	68	85 : 15	38
d	CCl_3	30		

Structural Assignments for Novel Hydroxypyrazoles.

Since nearly equal amounts of the two pyrazole isomers were formed in the synthesis of the C_2F_5 example it was not possible to assign the structures of the two isomers by assuming that the major product was the 3-hydroxy isomer. Fortunately, the isomeric hydroxypyrazoles differed greatly in physical and spectroscopic properties, and the structures could be assigned by analogy to the CF_3 examples as shown in Table II.

Table II. Physical and Spectroscopic Properties of 3- and 5-Hydroxypyrazoles

R_X	CF_3		C_2F_5		CF_2Cl	
	2a	**3a**	**2b**	**3b**	**2c**	**3c**
-OH Isomer	3	5	3	5	3	5
GC Ret. Time (min) [a]	1.42	4.38	1.26	4.51	2.82	3.93
Tlc Rf [b]	0.49	0.19	0.45	0.29	0.45	0.20
Sol. in Aq.-$NaHCO_3$	-	+	-	+	-	+
mp (°C)	129.5-131	172-175	117-121	183-188	124-125	168
Pmr, ring CH (ppm)	6.10	5.72	6.06	5.78	6.01	5.74
Fmr, $-CF_2-Y$ (ppm)	-60.5 (Y=F)	-62.4	-109.5 (Y=CF_3)	-112.2	-47.0 (Y=Cl)	-46.5
Cmr, ring CH (ppm)	93.2	85.4	94.6	86.3	92.5	84.9

[a] 3% OV-17, 100°-300°. [b] Silica gel, 1:1 hexane-ethyl acetate.

The C_2F_5 and CF_2Cl substituted hydroxypyrazoles are compared with the known CF_3 case [2]. The 5-hydroxy isomers **3b** and **3c** were either isolated from the mixtures of products formed from the enol ethers, or were synthesized from the corresponding β-ketoesters. The 3-hydroxy isomers were consistently more volatile, less polar, less acidic, and lower melting than the corresponding 5-hydroxy isomers. The nmr signals of the unsubstituted ring carbon

and its attached proton appeared at lower field in the 3-hydroxy isomers, and the signal from the fluorine attached to the carbon attached to the ring also appeared at lower field in the 3-hydroxy isomers.

Discussion.

The regiochemical outcome of the synthesis from α,β-unsaturated esters *vs.* that from β-ketoesters is probably based on the site of initial attack of the nucleophile. The more electron-rich nitrogen of methylhydrazine prefers to attack the α,β-unsaturated carbonyl system in a Michael (1,4) sense rather than in a 1,2 sense. The unsubstituted nitrogen is then brought into close proximity to the carbonyl carbon and completes the cyclization rapidly with expulsion of alcohol. While the same argument can be made for attack on the ketone carbonyl of a β-ketoester, attack of the substituted nitrogen gives a hemiaminal which can revert to starting materials. The unsubstituted nitrogen can attack the ketone and lead to imine formation, a pathway not available in the former case. While this argument is not rigorously supported by data, it does provide a useful conceptual framework for the reactions under study.

The failure of alkyl-substituted enol ethers **17** to give predominantly 3-hydroxypyrazoles points to the fact that merely providing an α,β-unsaturated carbonyl system as a Michael acceptor is not sufficient to induce the more nucleophilic nitrogen of the alkylhydrazine to attack the electrophile at the β-position. It appears that this position must be further activated by an electron-withdrawing substituent such as a haloalkyl group. Furthermore, as may be seen from Table I, the steric bulk of the β-substituent appears to also influence the ease of attack at that position.

Conclusions.

Four different but related compounds were found which could be used as starting materials for the synthesis of hydroxypyrazoles bearing haloalkyl substituents. All of these, when reacted with an alkylhydrazine, gave a mixture of isomers which strongly favored the 3-hydroxy isomer. Some of the factors influencing the regiochemistry of this addition were determined. Thus, these routes provide a complement to the well-known reaction of alkylhydrazines with β-ketoesters, which gives predominantly the 5-hydroxy isomers.

EXPERIMENTAL

General.

Melting points were obtained on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The pmr, cmr, and fmr spectra were obtained in chloroform-*d* on either a Varian EM-360 operating at a proton frequency of 60 MHz (CW pmr and fmr) or a Bruker WM-360 spectrometer operating at a proton frequency of 360 MHz in the pulsed Fourier transform mode (pmr and cmr); chemical shifts are reported as ppm (δ) downfield from internal standard tetramethylsilane for pmr and cmr spectra, and as ppm (δ) downfield from internal standard fluorotrichloromethane (negative chemical shift upfield) for fmr spectra. Thin layer chromatography was carried out on silica gel. Gas chromatography was carried out on a 4 ft x 1/8 in glass column packed with 3% OV-101 on Chromosorb W. Fluorinated acetoacetates were purchased from Fairfield Chemical Co., and methylhydrazine was purchased from Aldrich Chemical Co.

4,5-Dihydro-1,3-diphenyl-5-(trifluoromethyl)-1*H*-pyrazole (**7**).

The literature procedure reported [6] to give **6** was followed starting from 0.05 mole of **5**. The crude solid product was recrystallized from ethanol to give 4.75 g of a bright yellow solid, mp 113-115°. A second crop gave 0.68 g, mp 112-113°; combined yield of the two crops was 37%; pmr: δ 7.73-6.89 (m, 10H), 4.65 (ddq, J = 4.9, 11.5, 11, 1H), 3.47 (dd, J = 11, 18, 1H), 3.33 (dd, J = 1, 4.9, 1H); cmr: (carbon type from partially proton-decoupled spectrum) δ 148.9 (C), 145.5 (C), 131.2 (C), 129.5 (CH), 129.1 (CH), 128.5 (CH), 126.1 (CH), 125.0 (q, CF_3), 120.8 (CH), 114.1 (CH), 61.1 (q, *C*H-CF_3), 34.688 (CH_2); fmr: δ −74.7 (d); ms: m/z 290 (M^+-CF_3).

Anal. Calcd. for $C_{16}H_{13}F_3N_2$: C, 66.20; H, 4.51; N, 9.65. Found: C, 66.30; H, 4.51; N, 9.64.

1-Methyl-5-trifluoromethyl-2,3,4,5-tetrahydropyrazol-3-one (**9**).

A flask containing 9.2 g (0.20 mole) of methylhydrazine was cooled in an ice bath, and 33.6 g (0.20 mole) of **8** [8] was added dropwise with stirring at a rate such that the internal temperature did not exceed 20°. After addition was complete and the exotherm subsided the ice bath was removed and the reaction, which had become a solid mass, was allowed to stand overnight. The crude product was recrystallized from methylcyclohexane-ether to give two crops of product; first crop, 13.4 g of white solid, mp 98-99°; second crop, 15.85 g of pale yellow solid, mp 83-86°. The pmr analysis showed that the first crop was a single product, **9**, and that the second crop was an 8:1 mixture of **9** and an isomeric product, probably **10**, but this by-product was not isolated or fully characterized. The combined yield of **9** in the two crops was 88%; pmr: δ 9.5-8.5 (b, 1H), 3.48 (m, 1H), 3.02 (dd, J = 9.4, 17.0, 1H), 2.65 (s, 3H), 2.47 (dd, J = 6, 17.0, 1H); fmr: δ −77 (d); ms: m/z (relative intensity) [CI] 169 (M^++1); [EI] 168 (78) (M+), 149 (4), 99 (100); R_f: 0.40 (19:1 ethyl acetate-methanol).

Anal. Calcd. for $C_5H_7F_3N_2O$: C, 35.72; H, 4.20; N, 16.66. Found: C, 35.51; H, 4.13; N, 16.42.

Compound **10** had pmr: δ 3.10 (s); fmr δ −78.3 (d); ms: m/z (relative intensity) [EI] 168 (100) (M+), 99 (43); R_f: 0.29 (19:1 ethyl acetate-methanol).

1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-ol (**2a**).

Method A. Oxidation of **9** to **2a**.

A mixture of 0.168 g (1.0 mmoles) of **9** and 0.541 g (2.0 mmoles) of iron(III) chloride hexahydrate in 2.5 ml of ethanol was heated to reflux for 8 hours then allowed to stand at ambient temperature 48 hours. The ethanol was evaporated and the black residue taken up in 5% aqueous sodium hydroxide. The aqueous solution was washed once with dichloromethane, then acidified with concentrated hydrochloric acid. The acidic solution was extracted twice with dichloromethane, dried over anhydrous sodium sulfate, filtered, and evaporated. The solid residue was recrystallized from methylcyclohexane to give colorless prisms, mp 128-130°. Upon admixture with authentic **2a** [2], mp

130-130.5°; upon admixture with authentic **3a** [2], mp 118-120°.

Method B. Synthesis of **2a** from Dibromide **11**.

A solution of 73.7 g (1.6 moles) of methylhydrazine in 500 ml of tetrahydrofuran was placed in a flask equipped with a mechanical stirrer, thermometer, and dropping funnel. The mixture was cooled in an ice bath and 164.0 g (0.5 mole) dibromide **11** [15] was added dropwise with stirring and ice cooling over 90 minutes so that the temperature remained at 5-10°. After stirring an additional 90 minutes at ice bath temperature the reaction was allowed to come to ambient temperature overnight. The white suspension was filtered and the solid rinsed with tetrahydrofuran. After drying 114.4 g methylhydrazine hydrobromide was recovered. The filtrate was evaporated to give 84.9 g of a pasty yellow solid. This material was triturated three times with hot methylcyclohexane. Cooling of the combined extracts gave 59.8 g (72% yield) of **2a**, mp 129.5-130.5°.

Method C. Synthesis of **2a** from Enol Ether **15**. Part 1. 3-Methoxy-4,4,4-trifluoro-2-butenoic Acid Ethyl Ester (**15a**).

A solution of 184 g (1.0 mole) of ethyl 4,4,4-trifluoroacetoacetate (**4**) in 1 ℓ of acetone was prepared in a 3 ℓ flask equipped with mechanical stirrer, drying tube, and thermometer. To this solution was added 276 g (2.0 moles) of anhydrous potassium carbonate, and the solution was stirred. A rise in temperature to about 35° was observed. To this stirred mixture was added 252 g (2.0 moles) of dimethyl sulfate, and stirring was continued at 200-300 rpm. The reaction was monitored by fmr of filtered aliquots in acetone; the starting material appeared as two singlets at δ −75.5 and δ −83.0, and the product appeared as a singlet at δ −72.7. The temperature fell slowly to ambient over 3 hours and was 73% complete at that time. After 20 hours no starting material remained by fmr. Diatomaceous earth was added and the reaction was filtered to remove the solids. The solvent was distilled off through a 3-stage Snyder column until the vapor temperature in the pot reached 100°. The residue was cooled and diluted with 500 ml of dichloromethane to precipitate any further dissolved solids. The solvent was again distilled off. The residue was transferred to a smaller flask with a few granules of anhydrous potassium carbonate and distilled at 120 Torr through a 30 cm column packed with 1/8 in glass helices. The product was collected at 90-91° after a small forerun. Distillation was stopped when the vapor temperature of the distillate reached 100°, when dimethyl sulfate was observed in the distillate. A total of 172.3 g of **15a** was obtained as a water-white mobile liquid (87% yield); pmr: δ 5.73 (s, 1H), 4.22 (q, J = 7, 2H), 3.97 (s, 3H), 1.23 (t, J = 7, 3H); fmr δ −72.7 (s). **NOTE**: Care must be exercised in handling the heated pot residue due to vapors of dimethyl sulfate. After cooling in the hood the excess was destroyed with methanolic sodium hydroxide.

Anal. Calcd. for $C_7H_9F_3O_3$: C, 42.53; H, 4.58. Found: C, 42.47; H, 4.5.

Part 2. Addition of Methylhydrazine to **15a**.

To a flask equipped with an addition funnel, magnetic stirrer, and internal thermocouple was added 12.7 g (0.275 mole) of methylhydrazine, and the flask was cooled in an ice bath. To this flask was added 49.5 g (0.25 mole) of enol ether **15a** dropwise with stirring at a rate to keep the temperature below 20°. When addition was complete the ice bath was removed, whereupon the temperature rose to 37°. The cloudy, dark red solution was stirred overnight at ambient temperature. Volatiles were removed on the rotary evaporator and under vacuum. The yellow residue was taken up in hot methylcyclohexane and recrystallized to give 30.1 g of **2a** in two crops (72% yield), mp 124-129°.

Method D. Synthesis of **2a** from Enamine **16**.

Into a round bottom flask equipped with an addition funnel, magnetic stirrer, and internal thermocouple and cooled in an ice bath was placed 6.0 g (0.032 mole) of enamine **16** [25] and 1.5 g (0.032 mole) of methylhydrazine was added dropwise over 5 minutes. The mixture was then brought to 60° until all of the starting materials had disappeared by fmr. Volatiles were removed on the rotary evaporator and under vacuum, and the residue was slurried in a saturated aqueous sodium bicarbonate solution. The insoluble solid was filtered and dried to give 2.60 g (49% yield) **2a** which was consistent with physical and spectroscopic properties of the previously prepared material.

1-Methyl-5-(pentafluoroethyl)-1*H*-pyrazol-3-ol (**2b**).

Prepared from the corresponding dibromide and methylhydrazine as in Method B; recrystallization gave 11.9 g (14% yield) of **2b** as a brown solid, mp 119-124°. Further data given in Table I.

Anal. Calcd. for $C_6H_5F_5N_2O$: C, 33.34; H, 2.33; N, 12.96. Found: C, 33.34; H, 2.35; N, 12.92.

3-Methoxy-4,4,5,5,5-pentafluoropent-2-enoic Acid Ethyl Ester (**15b**).

The enol ether was prepared on a 0.5 mole scale as in Method C Part 1 above. The residue after distillation of the acetone was taken up in 200 ml of ether and treated with 10 g of triethylamine. After 90 minutes gc analysis revealed that no dimethyl sulfate remained. The cloudy solution was washed twice with 100 ml of water, dried over anhydrous magnesium sulfate, filtered, and evaporated to give a residue which was distilled through a 10 cm Vigreux column to give 107.2 g (86% yield) of **15b**, bp 101-134° (120 Torr); pmr: δ 5.93 (s, 1H), 4.33 (q, J = 7, 2H), 4.08 (s, 3H), 1.32 (t, J = 7, 3H); fmr: δ −83 (t, 3F), −119.5 (q, 2F). Acceptable analysis not obtained.

1-Methyl-5-(pentafluoroethyl)-1*H*-pyrazol-3-ol (**2b**) and 1-Methyl-3-(pentafluoroethyl)-1*H*-pyrazol-5-ol (**3b**).

Prepared from **15b** and methylhydrazine by Method C Part 2 on a 0.25 mole scale. The residue was stirred with excess aqueous sodium bicarbonate solution to effect dissolution of the 5-hydroxy isomer **3b**. Filtration and drying gave 16.1 g (39% yield) of **2b**. Upon acidification of the filtrate 23.4 g (56% yield) of **3b** was isolated as a white solid, mp 183-188°; identical to an authentic sample prepared from 3-oxo-4,4,5,5,5-pentafluoropentanoic acid ethyl ester and methylhydrazine. Further data given in Table I.

Anal. Calcd. for $C_6H_5F_5N_2O$: C, 33.34; H, 2.33; N, 12.96. Found: C, 33.25; H, 2.34; N, 12.93.

1-Methyl-5-(chlorodifluoromethyl)-1*H*-pyrazol-3-ol (**2c**).

Prepared from the methyl ester of enol ether **15c**; prepared as for **15b**, bp 104-110°; pmr: δ 5.82 (s, 1H), 4.17 (s, 3H), 3.85 (s, 3H). The enol ether and methylhydrazine were reacted as in Method C Part 2. Recrystallization in several crops gave 17.4 g (38% yield) of **2c** as a white solid, mp 124-125°. Further data given in Table I.

Anal. Calcd. for $C_5H_5ClF_2N_2O$: C, 32.89; H, 2.76; N, 15.35. Found: C, 33.24; H, 2.82; N, 15.66.

1-Methyl-3-(chlorodifluoromethyl)-1*H*-pyrazol-5-ol (**3c**).

Prepared from 4-chloro-4,4-difluoro-3-oxobutanoic acid methyl

ester and methylhydrazine. Attempts to separate the isomers by dissolution in aqueous bicarbonate led to decomposition. Pyrazole **3c** was isolated by recrystallization from ethyl acetate as a white solid, mp 166-168°. Further data given in Table I.

Anal. Calcd. for $C_5H_5ClF_2N_2O$: C, 32.89; H, 2.76; N, 15.35. Found: C, 32.91; H, 2.78; N, 15.32.

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