(d, J = 8.4 Hz, 1 H, Ar(5)-H), 7.38 (dd, J = 8.4, 2.1 Hz, 1 H, Ar(6)-H), 7.87 (d, J = 2.1 Hz, 1 H, Ar(2)-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ 17.10 (q), 23.75 (q), 56.46 (q), 56.75 (q), 71.37 (d), 72.88 (s), 73.43 (d), 78.12 (d), 83.22 (d), 86.34 (s), 99.12 (t), 110.71 (d), 129.21 (d), 133.81 (s), 138.57 (d), 158.13 (s); exact mass calcd for $C_{16}H_{23}IO_6$ m/e 438.0539, found m/e 438.0555.

Acknowledgment. We thank the National Institutes of Health and National Science Foundation for generous support, Dr. Charles Cottrell and Mr. Richard Weisenberger for assistance in recording NMR and mass spectra at The Ohio State University Chemical Instrumentation Center, Mr. Carl Engleman for recording NMR spectra at The Ohio State University NMR Facility, and Dr. Kurt Loening for naming of compounds.

Registry No. **9**, 101977-77-9; **9** formate derivative, 143288-86-2; **10**, 101977-78-0; **11a**, 143191-27-9; **11b**, 143191-28-0; **11c**, 143288-87-3; **12c**, 143191-31-5; **13**, 143191-30-4; **14**, 143191-29-1; **15**, 143288-88-4; **16a**, 143288-89-5; **16b**, 143288-91-9; **16c**, 143288-94-2; **17a**, 143288-90-8; **17b**, 143288-92-0; **17c**, 143288-93-1; **18**, 143288-95-3; **19**, 143288-96-4; **20**, 143288-97-5; 3-*epi*-**20**, 143191-32-6; **21a**, 143288-98-6; **21b**, 143191-33-7; **22a**, 143191-42-8; **23a**, 143191-39-3; **23b**, 143191-46-2; **24a**, 143191-38-2; **24b**, 143191-45-1; **27**, 83569-29-3; **28**, 116696-37-8; **29**, 143191-34-8; **30** diethyl (*p*-methoxybenzyl)phosphonate adduct, 143191-37-1; α-**30**, 143191-35-9; β-**30**, 143191-36-0; **32a**, 143191-40-6; **32b**, 143191-47-3; **33a**, 143191-41-7; **33b**, 143191-48-4; **34**, 143191-44-0; ethyl 3-hydroxypropionate, 623-72-3; *N*-(*p*-methoxyphenyl)cinnamaldimine, 80542-40-1; diethyl (4-methoxybenzyl)phosphonate, 1145-93-3.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for selected compounds, crystallographic data for compounds **11a** and **33a**, and tabular NMR data for compounds **11a–11c**, **12c**, **16a–16c**, and **17a–17c** (82 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Cyclocondensation of Alkylhydrazines and β-Substituted Acetylenic Esters: Synthesis of 3-Hydroxypyrazoles[1]

Bruce C. Hamper,* Mitchell L. Kurtzweil, and James P. Beck

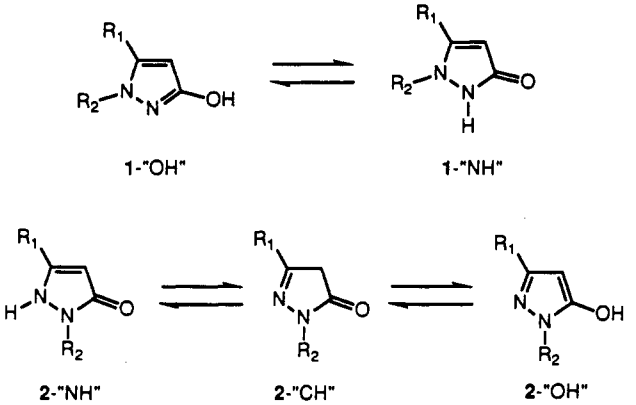
New Products Division, The Agricultural Group of Monsanto Company, 800 N. Lindbergh Boulevard, St. Louis, Missouri 63167

Received April 10, 1992

Addition of monosubstituted alkylhydrazines to acetylenic esters with either electron-withdrawing or sterically bulky β-substituents afforded 1-alkyl-3-hydroxy-5-substituted-pyrazoles **1** as the major regioisomeric product. By comparison, the classical cyclocondensation of alkylhydrazines with β-keto esters gives the regioisomeric pyrazol-5-ones **2**. The reaction solvent employed in these cyclocondensations can have a profound effect on regioisomeric product ratios. Addition of methylhydrazine to **5g** in methylene chloride gave regiospecific formation of pyrazolinone **2o**, whereas addition in water–methanol mixtures afforded hydroxypyrazole **1o** as the major product. Structural assignment of regioisomers **1** and **2** are based on ^{13}C NMR chemical shifts, long-range heteronuclear coupling constants, and comparisons with regiochemically known hydroxypyrazoles and/or pyrazolinones. Additions of acetylene **5b** to 1,1-dimethylhydrazine afforded either acyclic enehydrazone **12** or pyrazolium betaine **13** depending on the reaction conditions.

Introduction

Reactions of acetylenes and substituted hydrazines have been extensively studied as a means to prepare enehydrazines, hydrazones, and various cyclocondensation products.[2] Typically, cyclocondensations of either β-alkylacetylenic esters[3] or β-keto esters with alkylhydrazines[4] afford 1-substituted-pyrazolin-5-ones, **2**, as the major regioisomeric product. Surprisingly few reports have appeared describing the regioselective preparation of 3-hydroxypyrazoles, 1-"OH", or the tautomeric 3-pyrazolinones, 1-"NH", from acetylenic esters and alkylhydrazines.[5,6] Such reports have been limited to phenylhydrazine additions in the presence of base[7] and addition of alkylhydrazines to acetylene dicarboxylates.[8] A regiospecific synthesis of 3-hydroxy-5-arylpyrazoles from addition of methylhydrazine to arylglycidates followed by dehydration of the intermediate hydroxypyrazolinone has been reported.[9]



In view of the biological activity associated with a variety of pyrazole derivatives, the ability to prepare 1-alkyl-3-hydroxypyrazoles **1** seemed particularly attractive. De-

(1) Hamper, B. C.; Kurtzweil, M.; Beck, J.; Murray, T. Presented in part at the 13th International Congress of Heterocyclic Chemistry; Corvallis, OR, August 11–16, 1991.
(2) For a recent review, see: Sucrow, W. *Org. Prep. Proced. Int.* **1982**, *14*, 91–155.
(3) Butler, D. E.; DeWalt, H. A. *J. Org. Chem.* **1971**, *36*, 2542–2547.
(4) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, pp 167–344.
(5) Hamper, B. C. *J. Fluorine Chem.* **1990**, *48*, 123–131.
(6) A manuscript for the preparation of perfluoroalkyl-substituted pyrazoles **1** (e.g., R_1 = CF_3) from haloalkyl-substituted α,β-unsaturated esters is in preparation; Gaede, B. J., personal communication.
(7) (a) Nakamura, N.; Kishida, Y.; Ishida, N. *Chem. Pharm. Bull.* **1971**, *19*, 1389–1394. (b) Bouchet, P.; Elguero, J.; Pereillo, J.-M. *Bull. Soc. Chim. Fr.* **1973**, 2482–2485. (c) Al-Jallo, H. N. *Tetrahedron Lett.* **1970**, 875–876. (d) Badder, F. G.; El-Newaihy, M. F.; Salem, M. R. *J. Chem. Soc. C* **1969**, 836–838.
(8) (a) Sucrow, W.; Bredthauer, G. *Chem. Ber.* **1983**, *116*, 1520–1524. (b) Sucrow, W.; Mentzel, C.; Slopianka, M. *Chem. Ber.* **1974**, *107*, 1318–1328. (c) Fehlauer, A.; Grosz, K.; Slopianka, M.; Sucrow, W.; Lockley, W. J. S.; Lwowski, W. *Chem. Ber.* **1976**, *109*, 253–260.
(9) Sabaté-Alduy, C.; Bastide, J.; Bercot, P.; Lematre, J. *Bull. Soc. Chim. Fr.* **1974**, 1942–48.

0022-3263/92/1957-5680$03.00/0

Scheme I

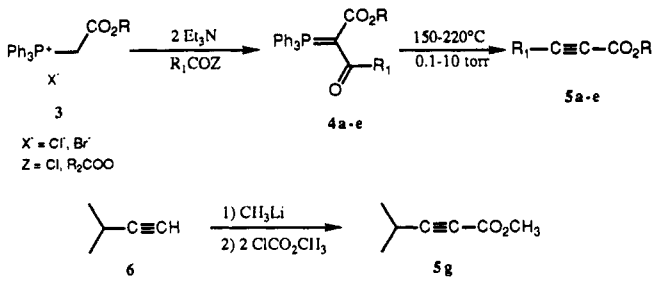


Table I. Preparation of Phosphoranes 4 and Acetylenic Esters 5

compd	R_1	R	% yield 4	% yield 5
a	CF_2CF_3	CH_2CH_3	69	95
b	CF_3	CH_2CH_3	93	89
c	CF_2Cl	CH_3	94	66
d	CF_2H	CH_2CH_3	78	64
e	$C(CH_3)_3$	CH_2CH_3	41	87
f	CH_3	CH_2CH_3		*a*
g	$CH(CH_3)_2$	CH_3		41[b]
h	Ph	CH_2CH_3		*a*

[a] Compounds **5f,h** were obtained from commercial sources (see the Experimental Section). [b] Compound **5g** was obtained by alkoxycarbonylation of the acetylide anion of 3-methyl-1-butyne.

rivatives of 3-hydroxypyrazoles have been employed for the preparation of herbicides including pyrazole phenyl ethers,[10] pyrazole benztriazole ethers,[11] and phenylpyrazoles.[12] Recently the pyrazole phenyl ether herbicides have been shown to inhibit protoporphyrinogen oxidase.[13] The 3-hydroxypyrazoles have been used as intermediates for carbamate insecticides,[14] ulcer inhibitors,[15] and cardiovascular agents.[16] In addition, they have also been used to prepare muscimol analogs[17] and have been identified as bacterial metabolites of antipyrine.[18]

We have previously described a facile preparation for a variety of (α-acylmethylene)phosphoranes **4** which are suitable precursors to β-substituted acetylenic esters.[19,20] These acetylenic esters **5** have shown synthetic utility for the preparation of multisubstituted heterocycles by both cycloaddition reactions[21] and cyclocondensations.[22] The

(10) (a) Lee, L. F.; Moedritzer, K.; Rogers, M. D. U.S. Patent 4,855,422, 1989. (b) Moedritzer, K.; Lee, L.; Rogers, M.; Anderson, D.; Singh, R.; Gaede, B.; Torrence, L. European Patent 295233, 1988; *Chem. Abstr.* **1989**, *111*, 23509x. (c) Moedritzer, K.; Rogers, M. European Patent 371947, 1990; *Chem. Abstr.* **1990**, *113*, 211973j.

(11) Pearson, D.; Mathews, C.; Cartwright, D.; Barnett, S. European Patent 442654, 1991; *Chem. Abstr.* **1991**, *115*, 256178m.

(12) Miura, J.; Oonishi, M.; Mabuchi, T.; Nishioka, H.; Kajioka, M.; Yanai, I. Japanese Patent 03072460, 1991; *Chem. Abstr.* **1991**, *115*, 49684h.

(13) Sherman, T. M.; Duke, M. V.; Clark, R. D.; Sanders, E. F.; Matsumoto, H.; Duke, S. O. *Pestic. Biochem. Physiol.* **1991**, *40*, 236–245.

(14) (a) Grauer, T.; Urwyler, H. U.S. Patent 3452043, 1969.

(15) Herter, R.; Schickaneder, H.; Moersdorf, P.; Postius, S.; Szelenyi, I.; Ahrens, K. U.S. Patent 4666921, 1987; *Chem. Abstr.* **1987**, *107*, 236703k.

(16) Dorn, H.; Ozegowski, R. DD Patent 242044, 1987; *Chem. Abstr.* **1987**, *107*, 59026u.

(17) Hans, H.; Krogsgaard-Larsen, P. *Acta Chem. Scand., Ser B* **1979**, *33*, 294–298.

(18) Sauber, K.; Mueller, R.; Keller, E.; Eberspaecher, J. *Z. Naturforsch., C: Biosci.* **1977**, *32C*, 557–62.

(19) Hamper, B. C. *J. Org. Chem.* **1988**, *53*, 5558–5562.

(20) Hamper, B. C. *Org. Synth.* **1991**, *70*, 246–255.

(21) (a) Tajammal, S.; Tipping, A. E. *J. Fluorine Chem.* **1990**, *47*, 45–57. (b) Kumabara, M.; Fununishi, K.; Mototeru, N.; Yamanaka, H. *J. Fluorine Chem.* **1988**, *41*, 227–239. (c) Nezis, A.; Fayn, J.; Cambon, A. *J. Fluorine Chem.* **1991**, *53*, 285–295.

(22) (a) Froissard, J.; Greiner, J.; Pastor, R. *J. Fluorine Chem.* **1981**, *17*, 249–263. (b) Chauvin, A.; Greiner, J.; Pastor, R.; Cambon, A. *Tetrahedron* **1986**, *42*, 663–668. (c) Chauvin, A.; Fabron, J.; Yahia, M. O. A.; Pastor, R.; Cambon, A. *Tetrahedron* **1990**, *46*, 6705–6714.

Table II. Addition of Alkylhydrazines to Acetylenic Esters 5

compd 1:2	R_1	R_2	ratio 1:2[a] H_2O–CH_3OH[b]	ratio 1:2[a] CH_2Cl_2[c]	% yield 1[d]
a	CF_2CF_3	CH_3	98:2	98:2	98
b	CF_3	CH_3	94:6	71:29	80
c	CF_2Cl	CH_3	95:5	95:5	79
d	CF_2H	CH_3	35:65	55:45	22[e]
e	CH_3	CH_3	0:100	0:100	85[f]
f	CF_3	Et	87:13		25
g	CF_3	*n*-propyl	90:10		25
h	CF_3	isopropyl	85:15		46
i	CF_3	*n*-butyl	75:25		42
j	CF_3	benzyl	55:45	30:70	32
k	CF_3	CH_2CH_2OH	80:20		62
m	CF_3	CH_2CF_3	0:100		
n	CF_3	*tert*-butyl	0:100		
o	isopropyl	CH_3	80:20	1:99	48
p	*tert*-butyl	CH_3	95:5	83:17	44
q	phenyl	CH_3	28:72		21
r	*n*-propyl	CH_3	5:95		

[a] Ratios of 1 and 2 were determined by concentration and extraction of the crude reaction mixtures and comparison of the ^{19}F and/or ^1H NMR resonances of the two products. [b] Reactions were carried out in methanol–water (1:1) at 0 °C. [c] Reactions were carried out in methylene chloride at −78 °C. [d] Except as noted, yields are of isolated product 1 from the reactions carried out in methanol–water. [e] Yield of **1d** isolated from the reaction carried out in CH_2Cl_2. [f] Yield of **2e**.

β-(perhaloalkyl)acetylenic esters undergo regiospecific cyclocondensation with methylhydrazine to afford 3-hydroxy-5-(perhaloalkyl)pyrazoles,[5] which are precursors to the aforementioned herbicidal phenylpyrazole ethers.[10] In this report, we investigate the cyclocondensation reactions of both fluorinated and nonfluorinated β-alkylacetylenic esters with mono- and disubstituted alkylhydrazines.

Results and Discussion

Preparation of β-Substituted Acetylenic Esters. Most of the acetylenic esters **5a–e** (Scheme I, Table I) were prepared by thermolysis of phosphoranes **4a–e**, as previously reported for trifluorobutynoate **5b**.[20,23] Thermolysis of (acylmethylene)phosphoranes **4a–e** was achieved by thoroughly drying the compounds to constant weight and subsequently heating under vacuum from 150 to 220 °C to afford the corresponding acetylenes **5a–e** and triphenylphosphine oxide. The fluorinated acetylenic esters **5a–d** are obtained directly from the thermolysis of the phosphoranes in 64–95% yields and do not require further purification. Preparation of nonfluorinated phosphorane **4e** and subsequent thermolysis to **5e** work equally well, although the yield of **4e** is somewhat lower than that of the halogenated phosphoranes **4a–d**. This method offers distinct cost advantages for the preparation of **5e** over the previous routes from the anion of *tert*-butylacetylene[24] or β-chloroalkylidene malonates[25] since it utilizes the significantly less expensive pivaloyl chloride as a starting material.

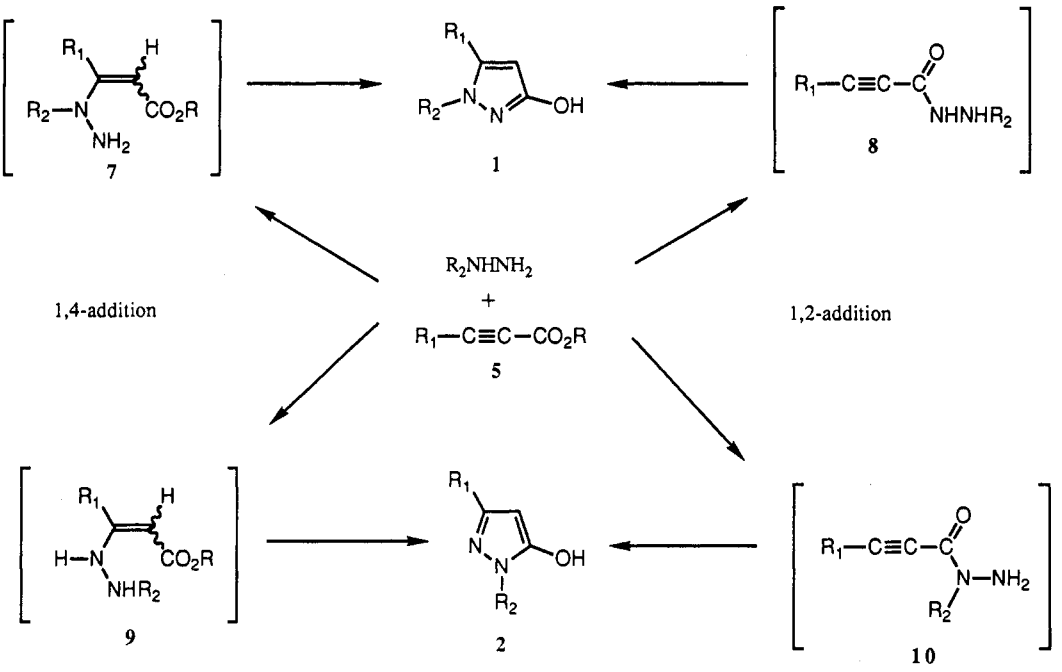
Although the phosphorane route can be used to prepare acetylenic esters such as ethyl 4,4-dimethyl-2-pentynoate, **5g**, the intermediate phosphorane **4g** could not be prepared directly from phosphonium salt **3** by treatment with isobutyryl chloride and triethylamine. Under these conditions, one obtains an allenecarboxylate ester due to the in situ formation of a ketene intermediate followed by the Wittig reaction.[26] By employing 1 equiv of triethylamine

(23) Huang, Y.; Shen, Y.; Xin, Y.; Fu, G.; Xu, Y. *Sci. Sin., Ser. B* **1982**, *25*, 557–593.

(24) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363–380.

(25) Hormi, O. *Org. Synth.* **1987**, *66*, 173–179.

Scheme II



in this reaction, we obtained an equimolar mixture of the desired phosphorane **4g** and phosphonium salt **3**. The phosphonium salt and **4g** can be separated by extraction; however, the yield suffers and for large-scale preparations the phosphorane invariably contains small amounts of the phosphonium salt which appears to have a detrimental effect on the yield of **5g** in the thermolysis step. Rather than use this route to prepare acetylene **5g**, we choose the more expedient treatment of terminal acetylene **6** with methyllithium followed by methyl chloroformate.[27]

Preparation of Pyrazoles 1 and 2. Addition of monoalkylhydrazines to **5** afforded regioisomeric hydroxypyrazoles **1** and **2** (Table II). For cases in which the acetylenic esters have either electron-withdrawing haloalkyl or sterically bulky R_1 substituents (**5a–e,g**), hydroxypyrazoles **1** are obtained as the major or sole regioisomeric product. By comparison, cyclocondensation of ethyl 4,4,4-trifluoroacetoacetate, in which R_1 is an electron-withdrawing CF_3 group, with methylhydrazine affords a mixture of **1b** and **2b** in which **2b** is the major product.[28] Likewise, addition of methylhydrazine to methyl pivaloylacetate gave **2p** as the only product.[29] Thus, the addition of monoalkylhydrazines to acetylenic esters **5a–d**, **5e**, and **5g** is complementary to the regiochemical outcome of classical cyclocondensations with β-keto esters.

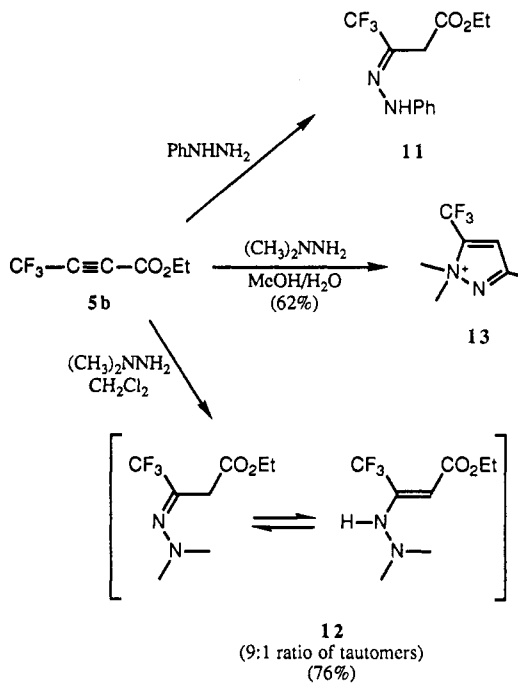
Highest yields were obtained for additions of methylhydrazine to (perhaloalkyl)acetylenic ester **5a–c**, particularly when methanol–water was employed as the reaction solvent. In these cases, **1a–c** were obtained as crystalline solids by simple filtration of the water–methanol reaction mixtures. The small amounts of the more water stable regioisomers **2a–c** remained in solution. Addition of other alkylhydrazines to **5b** afforded excellent regioselectivity of **1f–i**, although the yields were lower. Additions of methylhydrazine to nonfluorinated acetylenes can also provide novel 3-hydroxypyrazoles, such as **1o** and **1p** from isopropyl- and tert-butylacetylenes **5g** and **5e**, respectively. While the branched-chain alkylacetylenic esters were observed to give 3-hydroxypyrazoles, straight-chain ethyl 2-butynoate and 2-hexynoate gave exclusively 5-hydroxypyrazoles **2e** and **2r**. Reaction with ethyl phenylpropionate gave a mixture of isomers, which were separated chromatographically to give nearly a 1:3 ratio of isolated **1q** and **2q**, respectively.

The observed product selectivity is difficult to rationalize in view of the fact that there are four possible modes of initial addition of an alkylhydrazine to an acetylenic ester (Scheme II). Both 1,2 addition of the hydrazine to the ester carbonyl functionality or 1,4 addition[30] can give rise to **1** or **2** depending on which nitrogen of the hydrazine is involved in the initial nucleophilic attack. For methylhydrazine, the substituted nitorgen is more electron rich and in the case of 1,4 addition would be expected to give enehydrazine **7**. Addition of methylhydrazine to electron-deficient acetylenic esters such as dimethyl acetylenedicarboxylate have been reported to afford isolable enehydrazine intermediates such as **7** which can be treated with either heat or acid conditions to give hydroxypyrazoles.[8c] In all the cases of addition of methylhydrazine to acetylenic esters **5a–d** (R^1 is haloalkyl), however, we were unable to detect any of the intermediates **7–10** even at low temperatures. However, addition of dimethylhydrazine to **5b** ($R^1 = CF_3$) in CH_2Cl_2 affords a tautomeric mixture of the hydrazone and enehydrazine **12**, and under similar conditions, phenylhydrazine gives hydrazone **11** (Scheme III). Presumably, methylhydrazine also adds to acetylenic esters **5a–d** in a Michael sence (1,4 addition) to give intermediate **7** which rapidly undergoes cyclocondensation to pyrazole **1**. Addition of other alkyl-

(26) Lang, R. W.; Hansen, H. *Helv. Chim. Acta* **1980**, *44*, 438–455.
(27) Olomucki, M.; J. Y. LeGall *Org. Synth.* **1987**, *65*, 47–51.
(28) Lee, L. F.; Schleppnik, F. M.; Schneider, R. W.; Campbell, D. H. *J Heterocycl. Chem.* **1990**, *27*, 243–245.
(29) Friedmann, H.; Hansel, W. *Arch. Pharm. (Weinheim)* **1983**, *316*, 726–7.

(30) As a reviewer has suggested, the conjugate addition of the hydrazine to the acetylenic ester is formally a 1,2 addition across the carbon–carbon triple bond based on the product enehydrazines **7** and **9**. However, nucleophilic additions to the β position of α,β-unsaturated carbonyl systems are classified as 1,4 additions due to the mechanism. Initial attack of the nucleophile leads to an enolate ion which is protonated chiefly at oxygen and the resultant enol tautomerizes to the resultant product. March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 664.

Scheme III



hydrazines to **5b** is consistent with the enehydrazine intermediates **7** and **9**. The simple *n*-alkylhydrazines and isopropylhydrazine all resulted in 3-hydroxypyrazoles **1f–i,k** as the major regioisomeric product, while the more sterically hindered *tert*-butylhydrazine, which would be expected to initially give enehydrazine **9**, afforded **2n** as the only isolable product. Benzylhydrazine (entry j), which is less sterically bulky than the *tert*-butylhydrazine, gave mixtures of **1j** and **2j**. For (2,2,2-trifluoroethyl)hydrazine (entry m), both the steric bulk and the electron-withdrawing ability of the alkyl group suggest enehydrazine **9** as the most plausible intermediate since the unsubstituted nitrogen would be expected to be more nucleophilic and **2m** is the only product observed.

The nature of the R_1 substituent of the acetylenic ester also has a marked effect on regioselectivity. In the case of **5a–c** (R_1 is a perhaloalkyl group), pyrazole **1** is the major or sole regioisomeric product. As the size and electron-withdrawing ability of the R_1 group decreases, the amount of isomer **2** increases. Thus, for acetylene **5d** ($R_1 = CF_2H$) a mixture of products is obtained and for the nonhalogenated **5f** ($R_1 = CH_3$) only **2e** is obtained. As the steric bulk of the R_1 substituent increases, the amounts of hydroxypyrazole obtained also increase (entries o and p), and for the *tert*-butylacetylene **5g**, the 3-hydroxy isomer **1p** is the major product. For the nonfluorinated acetylenes **5e–i**, which are both less reactive and more sterically hindered in the β position, addition of the hydrazines to the carbonyl oxygen (1,2 addition) to give hydrazides **8** and **10** would be expected to play a greater role. In fact, acetylenic hydrazides have been isolated from addition of hydrazine to phenylpropiolate in alcohol.[7c]

A mixture of water and methanol employed as the reaction solvent provided nearly equal or greater regioselectivity for hydroxypyrazole **1** compared to methylene chloride in every case except **1d**. The solvent effect was most profound for addition of methylhydrazine to isopropylacetylenic ester **5g**, which affords exclusively **2o** in methylene chloride, while in methanol–water reaction medium **1o** is the major, although not the exclusive, isomeric product. Previous investigation[3] of additions of alkylhydrazines to **5g** had reported only formation of the 5-hydroxypyrazole **2o**. Addition of methylhydrazine to **5e** provided **1p** as the major product in either solvent, although the regioselectivity and product yield was greater in methanol–water. A strong solvent effect was also observed in the addition of dimethylhydrazine to **5b** (Scheme III). In water–methanol, one obtains a 62% yield of pyrazolium betaine **13a**, while in methylene chloride only **12** was observed. The preparation of pyrazolium betaines from 1,1-dilkylhydrazines and acetylenecarboxylic esters in protic solutions has been previously described.[31]

Spectral Properties of 1 and 2. In aprotic solvents, (perhaloalkyl)pyrazoles **1a–d, f–k** and **2a–d** exist primarily in the "OH" tautomeric form, as evidenced by the ^1H NMR spectra in $CDCl_3$ and solution IR in chloroform.[32] The pyrazoles **2b** and **2d** showed an absence of a methylene resonance in the ^1H NMR which would correspond to 2-"CH". **1b** and **2b** in chloroform show nearly identical solution IR spectra with an absence of carbonyl bands. Thus, both regioisomers exist primarily in the "OH" tautomeric form in aprotic solutions. The ^1H NMR spectra indicate that nonhalogenated pyrazoles **2o–r** exist as mixtures of pyrazolone "CH" and "OH" tautomers, while **1o–p** are primarily as the "OH" form.

The regioisomeric identify of 1-methylpyrazolin-5-ones, **2e,o–r**, prepared by cyclocondensation of methylhydrazine with keto esters, has been previously described.[29,33–35] These assignments are consistent with our observation of the 2-"CH" tautomers for these compounds by proton NMR. The perfluoro-substituted **2b** and **2d** do not exhibit appreciable amounts of the "CH" tautomers in proton NMR spectra, and regiochemistry was assigned on the basis of proton coupled ^{13}C NMR spectral data.[28] For pyrazoles **1a–d, 2b,** and **2d**, we investigated the long-range heteronuclear couplings in the two regioisomers (Table III). In the proton NMR spectra, the five- or six-bond coupling of fluorine to the *N*-methyl protons could be measured; however, the absolute values were similar for both isomers and too small (0.5–1.5 Hz) to be of diagnostic value. Four-bond fluorine coupling to the carbon of the *N*-methyl group was observed in the ^{13}C NMR spectra for **1b** and **1c** ($^4J_{CF}$ = 1.0 and 2.3 Hz, respectively) and was absent in the case of the corresponding isomer **2b**. However, it was not observed for either isomer **1a** or **1d**, and in these cases the line shape of the resonances indicates that the coupling must be smaller than 1.0 Hz.

Having previously determined the identity of the isomeric pairs **1b, 2b** and **1d, 2d** by spectral comparisons of long-range carbon–proton couplings,[5,28] we found comparative chemical shifts to be the most convenient method for regiochemical assignments of the fluoroalkyl substituted pyrazoles **1** and **2a–n**. For cases in which both regioisomers are available, small but consistent differences in chemical shift of the *N*-methyl group were observed in both the proton and carbon NMR spectra in which the *N*-methyl group of **2** is upfield of **1**. In addition, the C4 carbon resonance of isomer **2** is found to be upfield of corresponding resonance for isomer **1**. Except for the pair

(31) Sucrow, W.; Slopianka, M. *Chem. Ber.* **1978**, *111*, 780–790.
(32) The physical properties of the three tautomers of **2** are discussed in detail in Katritzky, A. R.; Maine, F. W. *Tetrahedron* **1964**, *20*, 299–314.
(33) Veibel, S.; Eggersen, K.; Linholt, S. C. *Acta Chem. Scan.* **1954**, *8*, 768–776.
(34) Carpino, L. A. *J. Am. Chem. Soc.* **1958**, *80*, 5796–5798.
(35) One report has appeared describing the preparation of "**1b**" as the sole product from the cyclocondensation of methyl 4,4,4-trifluoroacetoacetate and methylhydrazine; however, they provide no evidence for their assignment and the physical and spectral properties of their product are in agreement with those of **2b** rather than **1b**. Saloutin, V. I.; Kodess, M. I.; Fomin, A. N.; Selivanov, S. I.; Ershov, B. A.; Pashkevich, K. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, 399–402.

Table III. Proton and ^{13}C NMR Chemical Shifts of Hydroxypyrazoles 1 and 2[a]

compd	C3	C4	C5	NCH_3	H4	NCH_3
1a	161.1	94.8 (t) $^3J_{CF}$ = 5.0 Hz	130.2 (t) $^2J_{CF}$ = 29 Hz	38.5	6.03 (t) $^4J_{HF}$ = 1.0 Hz	3.80 (t) $^5J_{HF}$ = 1.5 Hz
1b	161.0	93.1 (q) $^3J_{CF}$ = 2.5 Hz	132.7 (q) $^2J_{CF}$ = 39 Hz	37.6 (q) $^4J_{CF}$ = 1.0 Hz	6.09 (q) $^4J_{HF}$ = 0.4 Hz	3.83 (q) $^5J_{HF}$ = 0.8 Hz
2b	140.3 (q) $^2J_{CF}$ = 38 Hz	85.4 (q) $^3J_{CF}$ = 2 Hz	153.8	34.1	5.80	3.66 (q) $^6J_{HF}$ = 0.6 Hz
1c	160.6	92.6 (t) $^3J_{CF}$ = 3.0 Hz	137.4 (t) $^2J_{CF}$ = 33 Hz	37.8 (t) $^4J_{CF}$ = 2.3 Hz	5.99	3.72 (t) $^5J_{HF}$ = 1.0 Hz
1d	161.4	92.0 (t) $^3J_{CF}$ = 4.2 Hz	137.5 (t)[b] $^2J_{CF}$ = 28 Hz	37.1	5.86 (t) $^4J_{HF}$ = 1.2 Hz	3.75 (t) $^5J_{HF}$ = 0.65 Hz
2d	145.2 (t) $^2J_{CF}$ = 29 Hz	84.2	153.7[c] $^3J_{CH}$ = 2.5 Hz $^2J_{CH}$ = 2.5 Hz	33.8	5.61 (t) $^4J_{HF}$ = 1.1 Hz	3.61 (t) $^6J_{HF}$ = 1.1 Hz
2e	145.5	87.0	155.3	32.0	5.11	3.38
1f	160.9	92.7 (q) $^3J_{CF}$ = 2.6 Hz	131.6 (q) $^2J_{CF}$ = 38.6 Hz		6.01	
1g	161.1	92.8 (q) $^3J_{CF}$ = 2.6 Hz	132.3 (q) $^2J_{CF}$ = 38.5 Hz		6.02	
1h	161.2	92.4 (q) $^3J_{CF}$ = 2.7 Hz	131.6 (q) $^2J_{CF}$ = 38 Hz		5.99	
1i	160.5	92.8 (q) $^3J_{CF}$ = 2.6 Hz	132.1 (q) $^2J_{CF}$ = 38.5		6.01	
1j	161.1	93.7 (q) $^3J_{CF}$ = 2.7 Hz	132.5 (q) $^2J_{CF}$ = 38.6		6.12	
2j	140.8 (q) $^2J_{CF}$ = 37.7 Hz	85.6 (q) $^3J_{CF}$ = 2.0 Hz	153.5		5.86	
1k	161.1	93.0 (q) $^3J_{CF}$ = 2.5 Hz	132.0 (q) $^2J_{CF}$ = 38.6		6.02	
2k	140.4 (q) $^2J_{CF}$ = 37.5 Hz	85.5 (q) $^3J_{CF}$ = 2.2 Hz	153.8		5.75	
2m	142.3 (q) $^2J_{CF}$ = 38.0 Hz	85.0 (q) $^3J_{CF}$ = 2.0 Hz	154.8		5.86	
2n	138.5 (q) $^2J_{CF}$ = 37.6 Hz	86.8 (q) $^3J_{CF}$ = 2.1 Hz	154.1		5.77	
1o	161.4	87.0	151.2	34.7	5.36	3.59
2o[d]	163.6	38.1	172.3	31.1	3.19	3.28
1p	160.9	89.3	153.1	38.5	5.38	3.77
2p	158.3	82.7	172.2	31.8	5.20	3.45
1q	161.6	91.2	145.5	36.2	5.71	3.70
2q	147.6	83.2	153.2	33.2	5.79	3.56
2r	150.7	88.6	160.4	31.0	5.16	3.51

[a] Chemical shifts are of the "OH" or "NH" tautomers of 1 and 2, except as noted. The spectra were obtained in acetone-d_6 except for: 2e, 2p and 2q, DMSO-d_2; 1o, 2o and 2r, $CDCl_3$; 1p, acetone-d_6/DMSO-d_6. [b] In the proton coupled ^{13}C NMR, the C5 resonance appears as a triplet of multiplets (based on the nuclei involved, the first-order system would appear as a triplet of doublets of doublets of quartets, tddq). [c] In the proton coupled ^{13}C NMR, the C5 resonance appears as a quartet of doublets. [d] Compound 2o exists primarily as the pyrazolone "CH" tautomer in $CDCl_3$.

of isomers 1q and 2q, the chemical shift of the 4-H proton of 1 is downfield of 2. Comparisons of the 4-H proton chemical shifts of regioisomeric pyrazoles have been reported and correlated to a summation of empirical constants for each substituent.[36] However, these comparisons are difficult in the case of tautomeric pyrazolinones–hydroxypyrazoles due to different contributions from the tautomers. The most useful observation, however, is the significant differences observed for the C3 and C5 ring carbons, which allows regioisomeric assignment of these pyrazoles even in the absence of both isomers.[37] The ring carbon bearing the R_1 substituent (C5 for isomer 1 and C3 for 2) is easily identified by the two-bond carbon–fluorine coupling ($^2J_{CF}$ is 28–40 Hz). For the 3-hydroxy isomer 1, the C5 carbon has greater enehydrazine character, while the similarly substituted C3 carbon of isomer 2 has more hydrazone character. Thus, the carbon bearing of the R_1 substituent of 3-hydroxypyrazole 1 is upfield (130–138 ppm) of the R_1-substituted carbon of 5-hydroxypyrazole 2 (139–145 ppm). By an analogous argument, the C3 carbon of 1 is downfield (160–161 ppm) of the C5 carbon of 2 (154–155 ppm). For the nonfluorinated pyrazoles 1 and 2o–q, these chemical shift arguments for C3 and C5 still apply for comparisons of the R_1-substituted carbon of the pyrazole ring, but not for the hydroxy- or carbonyl-substituted carbon due to greater contributions of the 2-"NH" and -"CH" tautomers in the NMR spectra.

In summary, a convenient synthetic method has been developed for the preparation of 3-hydroxypyrazoles 1 having either perhaloalkyl or sterically bulky substituents in the 5-position of the pyrazole ring from β-substituted acetylenic esters. This route is complimentary to classical cyclocondensation of hydrazines with β-keto esters which typically provide the regioisomeric pyrazol-5-ones 2. In addition, isolation of 1 is operationally straightforward since the product can often be collected directly from the water–methanol reaction mixtures by filtration.

Experimental Section

General. All reactions involving air- or moisture-sensitive reagents and all atmospheric distillations were run under a nitrogen atmosphere. The solvents and reagents were of reagent grade or better. Anhydrous solvents were obtained from Aldrich (Sureseal bottles). Preparative liquid chromatographic separations were performed on a 2-in. × 22-in. radially compressed silica chromatography column obtained from Millipore, Waters Chromatography. Analytical liquid chromatography was performed

(36) Tensmeyer, L. G.; Ainsworth, C. *J. Org. Chem.* **1966**, *31*, 1878–1883.

(37) Sohar, P.; Feher, O.; Tihanyi, E. *Org. Magn. Reson.* **1979**, *12*, 205–208.

with 250-mm × 0.46-mm-i.d. columns containing 5-μm silica using hexane/2-propanol mixtures as the mobile phase. Gas chromatographic analysis was performed using a 30-m megabore column containng 1.5-μm DB-1. A temperature program was employed which had an initial temperature of 100 °C with a hold time of 1 min followed by an increase of 25 °C/min and a final temperature of 250 °C. All melting points were recorded on a capillary melting point apparatus and are uncorrected. Proton and ^{13}C NMR spectra are reported relative to the internal tetramethylsilane in ppm, whereas ^{31}P NMR spectra are reported relative to external standard 85% aqueous phosphoric acid and ^{19}F NMR relative to trichlorofluoromethane using trifluorotoluene (−63.76 ppm) as an external coaxial standard. Elemental analysis were performed by Atlantic Microlabs, Inc., or by Midwest Microlab. Ethyl 2-butynoate (**5f**), ethyl phenylpropiolate (**5h**), and ethyl 2-hexynoate (**5i**) were obtained from Aldrich Chemical Co. or Farchan Lab. Compounds **1a–d, 2d,e, 4b,** and **5b** were prepared as previously described.[5,19] Compound **2b** was prepared by the method of Lee et al.[28] Phosphoranes **4a–e** were prepared by our general procedure from phosphonium salts.[19] The acetylenes **5a–e** were prepared using the apparatus previously described for the thermolysis of **4b** to **5b**.[20]

4,4,5,5,5-Pentafluoro-3-oxo-2-(triphenylphosphoranylidene)pentanoic Acid, Ethyl Ester (4a). Using the procedure of Hamper,[19] the resultant oily solid was purified by trituration with water to afford 85.2 g (68.9%) of a pinkish-white, crystalline solid: mp 146–147.5 °C; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H), 3.80 (q, 2 H), 7.43–7.70 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 13.6, 60.1, 71.9 (d, $^1J_{CP}$ = 109 Hz), 109.1 (CF_2, tqd, $^1J_{CF}$ = 269 Hz, $^2J_{CF}$ = 35 Hz, $^3J_{CP}$ = 11 Hz), 118.6 (CF_3, qtd, $^1J_{CF}$ = 287 Hz, $^2J_{CF}$ = 36 Hz, $^4J_{CP}$ = 2 Hz), 123.9 (C1, $^1J_{CP}$ = 94 Hz), 128.9 (C2, C6, $^2J_{CP}$ = 13 Hz), 132.6 ($^4J_{CP}$ = 3 Hz), 133.3 ($^3J_{CP}$ = 10 Hz), 165.7 ($^2J_{CP}$ = 12 Hz), 176.0 (C=O, td, $^2J_{CF}$ = 25 Hz, $^2J_{CP}$ = 6 Hz); ^{19}F NMR ($CDCl_3$) δ −71.0 (J = 4 Hz), −80.5; ^{31}P NMR ($CDCl_3$) δ 19.6; MS (EI) 494 (M^+, 11), 449 (−OEt, 11), (−CF_2CF_3, 100); MS (DP/CI isobutane) 495 (M + 1). Anal. Calcd for $C_{25}H_{20}O_3P_1F_5$: C, 60.74; H, 4.08. Found: C, 60.82; H, 4.11.

Pentafluoro-2-pentynoic Acid, Ethyl Ester (5a). By employing a previously described[20] vacuum distillation apparatus equipped with a dry ice–acetone trap, **4a** (82.1 g, 166 mmol) was thermolyzed under reduced pressure (7–9 Torr). Once the distillation pot reached 140–150 °C, the solid phosphorane melted and evolution of acetylene began. The mixture was heated from 150 to 210 °C and the acetylene collected in the dry ice trap. After production of acetylene from the reaction pot had ceased, the cold trap was removed to afford 34.13 g (95.1%) of a clear, orange liquid. While this material proved to be analytically pure, a colorless liquid is obtained by distillation: bp_{760} 111–115 °C; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz), 4.34 (q, 2 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 63.9, 69.3 (C3, $^2J_{CF}$ = 37 Hz), 80.5 (C2, $^3J_{CF}$ = 5.4 Hz), 105.0 (tq, CF_2, $^1J_{CF}$ = 248 Hz, $^2J_{CF}$ = 43 Hz), 117.8 (qt, CF_3, $^1J_{CF}$ = 286 Hz, $^2J_{CF}$ = 36 Hz), 150.9 (C=O); ^{19}F NMR ($CDCl_3$) δ −85.17 (t, 3 F, $^3J_{FF}$ = 3.7 Hz), −104.47 (q, 2 F, $^3J_{FF}$ = 3.7 Hz). Anal. Calcd for $C_7H_5O_2F_5$: C, 38.91; H, 2.33. Found: C, 38.97; H, 2.36.

4-Methyl-2-pentynoic Acid, Methyl Ester (5g). The general procedure of Olomucki and LeGall was followed:[27] A solution of 3-methyl-1-butyne (8.0 g, 117 mmol) was prepared by careful addition of the acetylene to 40 mL of anhydrous ethyl ether at −78 °C. The stirred solution was treated with methyllithium (1.5 M, 75 mL, 117 mmol) dropwise over 1 h such that the temperature was maintained below −70 °C. After being stirred for 20 min, the mixture was treated dropwise with methyl chloroformate (15.45 mL, 200 mmol) and allowed to warm to room temperature overnight. The mixture was quenched with 40 mL of H_2O and extracted three times with ether (40 mL each). All three ether layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Vacuum distillation provided 5.97 g (40.5%) of the clear, colorless oil: bp_{30} 80 °C; ^1H NMR ($CDCl_3$) δ 1.14 (d, 6 H, J = 7 Hz), 2.60 (septet, 1 H, J = 7 Hz), 3.66 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 19.92, 21.20, 51.93 (C4), 71.56 (C2) 93.77 (C3), 153.79 (C1). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.59; H, 8.02.

Preparation of 1-Alkyl-3-hydroxypyrazoles. With the exceptions noted below, compounds **1f–k** and **2j–m** were prepared by the previously reported method for 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-ol (**1b**) from ethyl 4,4,4-trifluoro-2-butynoate (**5b**) and the appropriate alkylhyrazine.[5]

1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-ol (1b): mp 130.0–130.5 °C; (lit.[5,28] mp 129.5–131.5 °C) (GC t_R = 1.31), ^1H NMR ($CDCl_3$) δ 3.79 (s, 3 H), 5.98 (s, 1 H), 11.33 (brs, 1 H); IR (soln $CHCl_3$) 2380, 3020 (CH str), 3590, 3660.

1-Methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-ol (2b): mp 172–175 °C (lit.[28] mp 172–175 °C) (GC t_R = 2.44), ^1H NMR ($CDCl_3$) δ 3.71 (s, 3 H), 5.71 (s, 1 H), 11.70 (brs, 1 H); IR (soln $CHCl_3$) 2380, 3020 (CH str), 3590, 3660.

1-(1-Methylethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-ol (1h). A solution of isopropylhydrazine dihydrooxalate (5.0 g, 30 mmol) in 60 mL of water was treated with 25 mL of 2.5 M NaOH followed by 85 mL of methanol. The resultant mixture was filtered to remove salts, cooled in an ice water bath, and treated with ethyl 4,4,4-trifluoro-2-butynoate (4.4 mL, 30 mmol). After stirring overnight, the reaction mixture was diluted with water and extracted three times with ethyl acetate, and the combined organic extracts were dried and concentrated to afford an oil which crystallized on standing. Recrystallization from methylene chloride–hexanes afforded 2.75 g (46%, GC t_R = 4.37) of a white, crystalline solid: mp 105–107 °C; ^{19}F NMR (acetone-d_6) δ −60.6. Anal. Calcd for $C_7H_9N_2OF_3$: C, 43.40; H, 4.67; N, 14.43. Found: C, 43.35; H, 4.68; N, 14.42.

1-(Phenylmethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-ol (1j) and 1-(Phenylmethyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-ol (2j). To a solution of benzylhydrazine dihydrochloride (29.4 g, 0.15 mol) in 100 mL of methanol was added 17.2 mL (0.075 mol) of 25% of sodium methoxide with stirring. After 20 h, the precipitate was filtered and washed with methanol. The filtrate was added dropwise to a mixture of ethyl 4,4,4-trifluoro-2-butynoate (25.5 g, 0.15 mol) in 100 mL of 1:1 methanol–water at 5 °C. After being stirred overnight the reaction mixture was concentrated in vacuo and the resulting solid dissolved in ethyl acetate, washed with water, dried over magnesium sulfate, and concentrated. The mixture was fractionally crystallized from methylcyclohexane to afford 7.87 g (32%) of **1j** as an off-white solid: mp 125–126.5 °C; ^{19}F NMR (acetone-d_6) δ −60.1. Anal. Calcd for $C_{11}H_9N_2OF_3$: C, 54.55; H, 3.74; N, 11.57. Found: C, 54.38; H, 3.80; N, 11.56.

The mother liquors were concentrated and triturated with chloroform to afford 7.1 g (29%) of **2j**: mp 224.5–225.5 °C; ^{19}F NMR (DMSO-d_6) δ −61.4. Anal. Calcd for $C_{11}H_9N_2OF_3$: C, 54.55; H, 3.74; N, 11.57. Found: C, 54.02; H, 3.71; N, 11.48.

3-Hydroxy-5-(trifluoromethyl)-1*H*-pyrazole-1-ethanol (1k) and 5-Hydroxy-3-(trifluoromethyl)-1*H*-pyrazole-1-ethanol (2k). The reaction mixture (29.4 mmol) was concentrated in vacuo to give a pink oil which was dissolved in ether and extracted with a solution of $NaHCO_3$ (1.4 g, 19 mmol) in 50 mL of water. The organic layer was dried over magnesium sulfate and concentrated in vacuo and the resultant oil crystallized from ether–petroleum ether to afford 0.96 g (16.6%) of **1k** as a white crystalline solid: mp 89–90 °C; ^{19}F NMR (acetone-d_6) δ −60.1. Anal. Calcd for $C_6H_7N_2O_2F_3$: C, 36.74; H, 3.60; N, 14.28. Found: C, 36.66; H, 3.61; N, 14.23.

Acidification of the aqueous extract with 12 N HCl afforded an oil which was extracted with ether, dried over magnesium sulfate, and concentrated in vacuo to give a yellow oil which was crystallized from ether–petroleum ether to give 0.87 g (15.1%) the **2k**: mp 140–143 °C; ^{19}F NMR (acetone-d_6) δ −63.4. Anal. Calcd for $C_6H_7N_2O_2F_3$: C, 36.74; H, 3.60; N, 14.28. Found: C, 36.80; H, 3.60; N, 14.24.

1-Methyl-5-(1-methylethyl)-1*H*-pyrazol-3-ol (1o). A solution of 1.1 mL of methylhydrazine in 40 mL of water–methanol (1:1 solution) was treated with 2.7 g (21.9 mmol) of **5g**, and the reaction mixture was heated to reflux for 3 days. After allowing the mixture to cool, a crystalline product was collected, washed with cold water, and dried to afford 1.45 g (48.3%, GC t_R = 4.90) of a white, crystalline solid: mp 156.5–157.0 °C; IR (soln $CHCl_3$) 1560 (C=N), 2600, 2980 (CH str), 3160; MS (EI) 140 (M^+, 53), 125 (−CH_3, 100); MS (DP/CI isobutane) 141 (M + 1, 100). Anal. Calcd for $C_7H_{12}N_2O_1$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.88; H, 8.67; N, 20.03.

1-Methyl-3-(1-methylethyl)-1*H*-pyrazol-5-ol (2o). A solution of 1.1 mL of methylhydrazine in 20 mL of methylene chloride was cooled in an ice water bath and treated with 2.7 g (21.9 mmol) of **5g** and the ice bath removed. The reaction mixture was heated

to reflux for 24 h and allowed to cool. Concentration of the reaction mixture afforded 3.0 g of a yellow solid which was recrystallized from methylcyclohexane to afford 1.45 g (48.3%, GC t_R = 3.95) of a white, crystalline solid: mp 119–121.5 °C (lit.[29] mp 128 °C). In $CDCl_3$ at room temperature, a 60:40 mixture of tautomeric 5-pyrazolinone and pyrazol-5-ol is observed in the ^1H NMR spectra. At 55 °C, the major tautomer (90%) is the 5-pyrazolinone: ^1H NMR ($CDCl_3$, 55 °C) δ 1.20 (d, 6 H, J = 6 Hz), 2.69 (m, 1 H), 3.19 (s, 2 H), 3.28 (s, 3 H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 20.2, 30.6, 31.1, 38.1, 163.6, 172.3; MS (EI) 140 (M^+, 98), 125 (–CH_3, 100), 97 (14), 69 (78); MS (DP/CI isobutane) 141 (M + 100). Anal. Calcd for $C_7H_{12}N_2O_1$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.91; H, 8.66; N, 19.96.

5-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-3-ol (1p). A solution of 1.1 mL of methylhydrazine in 40 mL of water–methanol (1:1 solution) cooled in an ice water–acetone bath was treated with 3.38 g (21.9 mmol) of **5e** and the ice bath removed. The reaction mixture was heated to reflux for 3 days and allowed to cool. By diluting the mixture with water, a crystalline product was obtained which was collected, washed with water, and dried to afford 1.5 g (44.4%, CG t_R = 4.69) of a white, crystalline solid: mp 186–187 °C; IR (soln $CHCl_3$) 1560 (C=N), 2610, 2980 (CH str), 3070; MS (EI) 154 (M^+, 40), 139 (–CH_3, 100); MS (DP/CI isobutane) 155 (M + 1, 100). Anal. Calcd for $C_8H_{14}N_2O_1$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.38; H, 9.19; N, 18.16.

3-(1,1-Dimethylethyl)-1-methyl-1*H*-pyrazol-5-ol (2p). Purchased from Lancaster Synthesis as 3-*tert*-butyl-1-methyl-2-pyrazolin-5-one (CG t_R = 3.95): mp 150–152 °C (lit.[29] mp 155 °C); ^1H NMR (DMSO-d_6) δ 1.20 (s, 9 H), 3.45 (s, 3 H), 5.20 (s, 1 H).

1-Methyl-5-phenyl-1*H*-pyrazol-3-ol (1q) and 1-Methyl-3-phenyl-1*H*-pyrazol-5-ol (2q). A solution of 1.1 mL of methylhydrazine in 40 mL of water–methanol (1:1 solution) was treated with 3.4 mL (3.6 g, 20.6 mmol) of ethyl phenylpropiolate and the reaction mixture heated to 60 °C for 6 h. After the mixture was allowed to cool, a solid precipitate was collected, washed with cold water, and dried. The solid was triturated with a mixture of ethyl acetate, methylene chloride, and dimethyl sulfoxide, collected, and dried to afford 1.76 g (CG t_R = 5.17) of **2q** as a white solid: mp 208–212 °C (lit.[34] mp 214–216 °C). Anal. Calcd for $C_{10}H_{10}N_2O_1$: C, 68.95; H, 5.79; N, 16.08. Found: C, C, 68.73; H, 5.83; N, 15.94.

The combined filtrates from the reaction mixture and trituration of **2q** were concentrated and chromatographed (2-in. × 22-in. silica column, 15% isopropyl alcohol in hexanes) to afford two fractions. The more retained chromatographic fraction (k', 4.7) was concentrated and dried to afford 0.27 g of **2q** giving a total yield of 2.03 g (56.6%) of this isomer. Concentration of the less retained chromatographic fraction (k', 1.7) afforded 0.77 g (21.5%, GC t_R = 5.00) of **1q** as a white, crystalline solid: mp 161.5–163.0 °C (lit.[9] mp 163 °C). Anal. Calcd for $C_{10}H_{10}N_2O_1$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.89; H, 5.82; N, 16.05.

4,4,4-Trifluoro-3-(phenylhydrazono)butanoic Acid, Ethyl Ester (11). A solution of phenylhydrazine (5.45 g, 50.4 mmol) in 40 mL of CH_2Cl_2 was cooled in a dry ice–acetone bath and treated dropwise with **5b** (8.1 mL, 55.6 mmol) such that the reaction temperature was kept below –30 °C. After 1 h of stirring the ice bath was removed and the mixture allowed to warm to room temperature. Concentration in vacuo gave a yellow solid which was crystallized in hexanes to yield 11.7 g (84.6%) of a white, crystalline solid: mp 59.5–60.0 °C; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 3.41 (s, 2 H), 4.15 (q, 2 H, J = 7 Hz), 6.93 (t, 1 H, J = 7.3 Hz), 7.11 (d, 2 H, J = 7.8 Hz), 7.25 (t, 2 H, J = 7.9 Hz), 9.01 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 32.0 (CH_2), 62.5 (CH_2), 114.1 (C2, C6), 121.8 (CF_3, $^1J_{CF}$ = 272 Hz), 122.4 (C4), 124.3 (C=N, $^2J_{CF}$ = 36 Hz), 129.5 (C3, C5), 143.6 (C1), 168.2 (C=O); ^{19}F NMR ($CDCl_3$) δ –68.5. Anal. Calcd for $C_{12}H_{13}O_2N_2F_3$: C, 52.56; H, 4.78; N, 10.21. Found: C, 52.63; H, 4.80; N, 10.22.

3-(Dimethylhydrazono)-4,4,4-trifluorobutanoic Acid, Ethyl Ester, Mixture with 10% Ethyl (*Z*)-3-(Dimethylhydrazono)-4,4,4-trifluoro-2-butenoate (12). To a stirred solution of 1,1-dimethylhydrazine (3.8 mL, 50 mmol) in 30 mL of methylene chloride cooled in an ice–acetone bath was added **5b** (7.3 mL, 50 mmol). The solution stirred overnight and was concd in vacuo to afford a crude oil. Vacuum distillation afforded 8.6 g (76%) of a clear colorless oil: $bp_{0.5}$ 44–48 °C; ^{19}F NMR ($CDCl_3$) δ –66.81 (d, 10%, ^4J = 2 Hz), –68.78 (s, 90%); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz), 2.83 (s, 6 H), 3.52 (s, 2 H), 4.19 (q, 2 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 33.3 (CH_2), 46.8 (NCH_3), 61.6 (CH_2), 121.2 (CF_3, $^1J_{CF}$ = 275 Hz), 136.4 (C=N, $^2J_{CF}$ = 33 Hz), 168.0 (C=O); IR (neat) 2980 (CH, str), 1740 (C=O), 1675, 1630. Anal. Calcd for $C_8H_{13}F_3N_2O_2$: C, 42.48; H, 5.79; N, 12.38. Found: C, 42.55; H, 5.83; N, 12.37.

2,3-Dihydro-1,1-dimethyl-3-oxo-5-(trifluoromethyl)-1*H*-pyrazolium Hydroxide, Inner Salt (13). A mixture of **5b** (7.3 mL, 50 mmol) in 40 mL of methanol–water (1:1) was cooled in an ice water bath and treated dropwise with a solution of 1,1-dimethylhydrazine (3.8 mL, 50 mmol) in 20 mL of methanol–water (1:1). After 30 min of stirring, the ice bath was removed and the two phase mixture stirred for two h. The resultant solution was concentrated in vacuo to afford a crystalline solid. Trituration in methanol–acetone afforded 5.59 g (62.1%) of a white, crystalline solid: mp 176–178 °C; ^1H NMR (CD_3OD) δ 3.58 (s, 6 H), 7.24 (s, 1 H); ^{13}C NMR (CD_3OD) δ 56.1 (CH_3's), 120.3 (CF_3, $^1J_{CF}$ = 272 Hz), 132.6 (C4, $^3J_{CF}$ = 3 Hz), 152.0 (C5, $^2J_{CF}$ = 39 Hz), 173.9 (C=O); ^{19}F NMR (CD_3OD) δ –61.59; MS(EI) 180 (M^+, 45), 165 (–CH_3, 21); MS (CI) 181 (M + 1). Anal. Calcd for $C_6H_7O_1N_2F_3$: C, 40.01; H, 3.92; N, 15.55. Found: C, 40.11; H, 3.97; N, 15.54.

Acknowledgment. The authors wish to thank M. Dahl (Monsanto) for obtaining the mass spectra and Dr. Kurt Moedritzer, Dr. Bruce J. Gaede, and Dr. Pana Charumilind for helpful discussions.

Supplementary Material Available: Complete ^1H and ^{13}C NMR data for **1f–k, 1o–q, 2j–r, 4c–e, 5c–e** and an experimental description of the preparation of **4c–e** and **5c–e** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.