Reaction of 4-Hydroxy-5-oximino-3-thiophenecarboxylates with Hydrazines. Formation of Pyrazolylthiohydroxamic Acids

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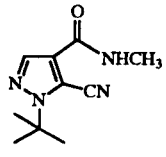
Received August 7, 1996

The reactions of 4-hydroxy-5-oximino-3-thiophenecarboxylates with hydrazine and substituted hydrazines have been investigated. The products of the reactions have been shown to be pyrazole-3- or 5-thiohydroxamic acids rather than the hydrazones previously described by Benary and Silberstrom. Two alternate mechanisms are proposed which account for the regiochemical outcome. The structures of the pyrazole-3- and 5-thiohydroxamic acids and corresponding nitriles have been proven by independent synthesis, comparison to known compounds, and by proton and carbon magnetic resonance and long range HETCOR experiments.

J. Heterocyclic Chem., **34**, 413 (1997).

Introduction.

Several reports have appeared in recent years detailing the fungicidal [1], herbicidal [2,3], and pharmaceutical [4,5] activity of pyrazoles. As part of our research on the herbicidal pyrazoles, we have been interested in synthetic methods which might apply to the synthesis of 5-cyanopyrazoles such as 5-cyano-1-(1,1-dimethylethyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide **1** [6], the corresponding ester, and the corresponding 1-phenyl and 1-methyl analogs.



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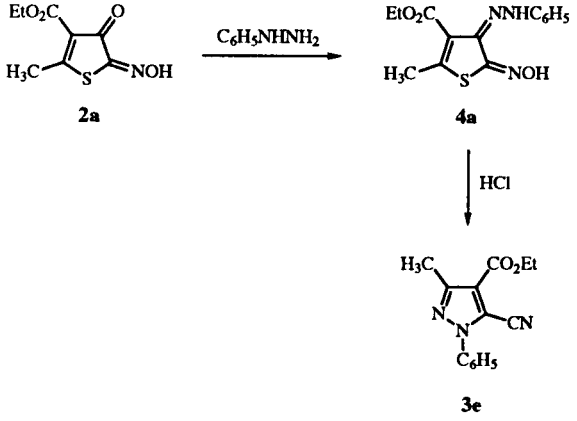
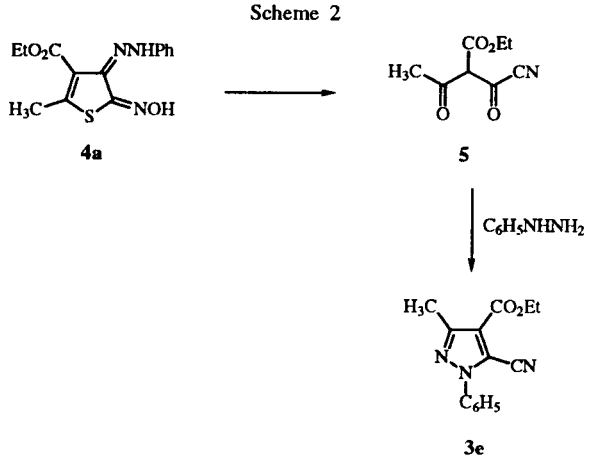
In the course of reviewing the literature in this area, we came across a report by Benary and Silberstrom detailing the conversion of 4,5-dihydro-5-hydroximino-4-oxo-2-methyl-3-thiophenecarboxylic acid ethyl ester **2a** to ethyl 5-cyano-1-phenyl-3-methyl-1*H*-pyrazole-4-carboxylate **3e** [7] (Scheme 1).

Scheme 1



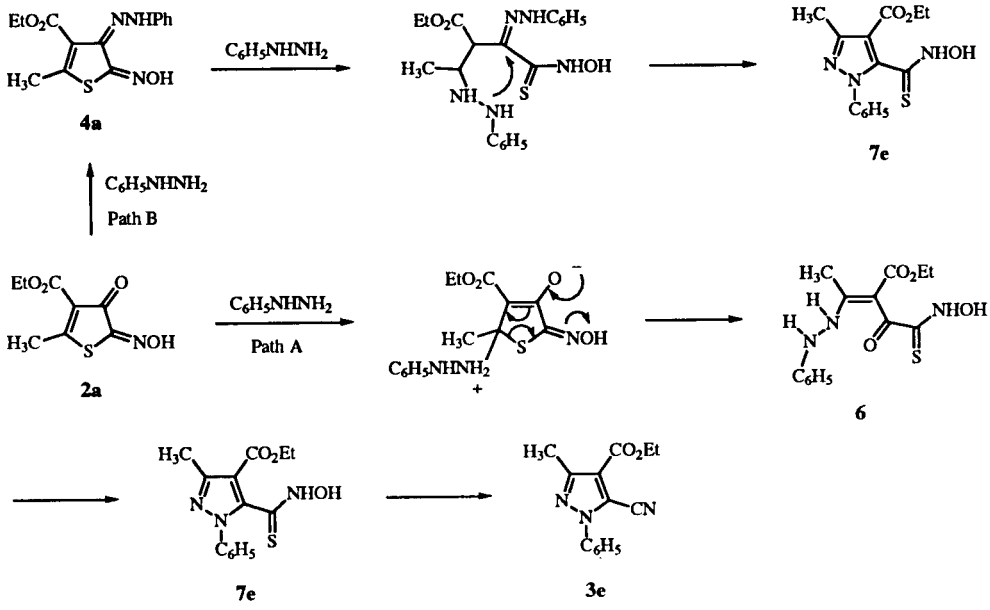
Benary and Silberstrom also described the isolation and identification of the phenylhydrazone **4a** and its decomposition in the presence of hydrochloric acid to give **3e**. They proposed that, in the presence of acid, **4a** was converted to the acylcyanide **5** and phenylhydrazine, and that the recombination of phenylhydrazine and **5** led to the formation of 5-cyanopyrazole **3e** (Scheme 2). This mechanism seemed very unlikely to us and led us to propose the mechanism shown in Scheme 3.

Scheme 2



We felt that phenylhydrazine would more likely react with **2a** by conjugate addition to give a ring-opened addition product **6** which could undergo an intramolecular cyclization to give thiohydroxamic acid **7e** (Scheme 3, Path A). Since the conversion of thiohydroxamic acids to nitriles in the presence of acid with elimination of sulfur and water is known to be facile, the thiohydroxamic acid **7e** under acidic reaction conditions would be expected to convert to the corresponding nitrile **3e** [8]. The conjugate addition of hydroxylamine [9] and alkyl and arylhydrazines [10] to ethoxycarbonyl-3(2*H*)-furanones and 2,3-dihydro-4*H*-pyran-4-ones [11] has been observed and lends support to our proposal.

Scheme 3

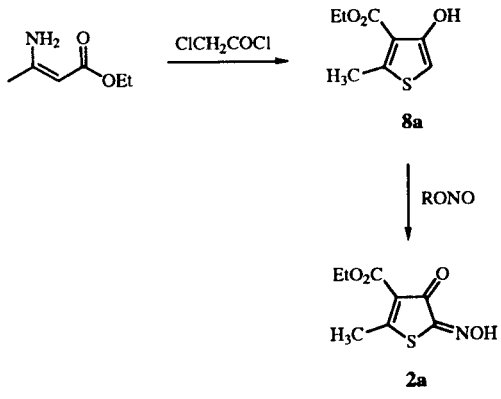


As Deshayes and Gelin [11] have proposed for 2,3-dihydro-4*H*-pyran-4-ones, however, conjugate addition of phenylhydrazine to **2a** could compete with phenylhydrazone formation. Therefore, it is also conceivable that conjugate addition of phenylhydrazine to the phenylhydrazone **4a** could take place leading to ring opening and cyclization to also give **7e** (Scheme 3, Path B).

Reexamination of the Reaction of **2a** with Phenylhydrazine.

We initially set out to repeat the work of Benary and Silberstrom and examine the so-called phenylhydrazone intermediate. The 5-hydroximino-4-oxothiophene **2a** starting material was prepared by nitrosation of ethyl 4-hydroxy-2-methyl-3-thiophenecarboxylate **8a** (Scheme 4). Compound **8a** was prepared by a literature method from ethyl 2-methyl-2-aminoacrylate and chloroacetyl chloride [12].

Scheme 4



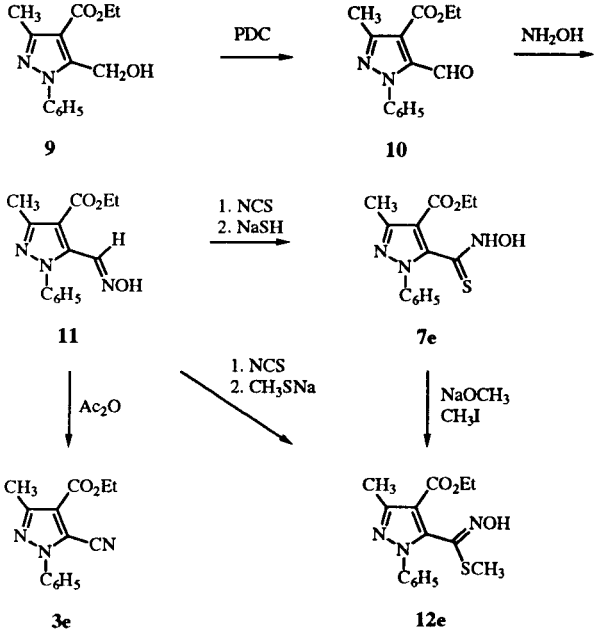
When **2a** was treated with phenylhydrazine in acetic acid according to the procedure described by Benary and Silberstrom [7], a product was isolated in 83% yield which melted at 158-159°, similar to that reported by Benary (152-153°) for his purported phenylhydrazone. The elemental analysis for the compound was correct for either the phenylhydrazone **4a** or the thiohydroxamic acid **7e**, which are isomeric. The mass spectrum indicated the presence of a molecular ion at m/z 305 and a fragment at m/z 255 (M-50), indicating possible loss of elemental sulfur and water either prior to or during the running of the mass spectrum. The ^{13}C nmr spectrum clearly indicated the presence of a carbon sulfur double bond (150 ppm), but also indicated varying levels of a nitrile (110 ppm), depending on the length of time between sample dissolution in deuteriodimethyl sulfoxide or deuteriochloroform and running the spectrum. The ir spectrum indicated the presence of an ester and probable OH and NH groups, but the ir spectrum was not particularly helpful in distinguishing between the two possibilities.

We were able to derivatize the Benary intermediate by reaction with sodium methoxide and iodomethane in methanol to give a more stable intermediate, mp 161-162°, which by ^1H nmr contained one additional methyl group.

The Benary intermediate was conclusively identified by independent synthesis as the thiohydroxamic acid **7e** [13,14] (Scheme 5). Thus, oxidation of 1-phenyl-4-ethoxycarbonyl-5-hydroxymethyl-3-methylpyrazole **9** [16] using pyridinium dichromate gave the aldehyde **10** which was converted to the oxime **11** by reaction with hydroxylamine. Chlorination of **11** with *N*-chlorosuccinimide [17]

followed by reaction of the intermediate chlorooxime with sodium hydrosulfide [18,14] gave **7e**. This compound was found to be identical to the intermediate prepared by Benary and Silberstrom [7] and previously misidentified as **4a**. Dehydration of the oxime **11** by heating in acetic anhydride (Scheme 5) gave 5-cyano-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester **3e**, identical to **3e** prepared by the Benary method.

Scheme 5

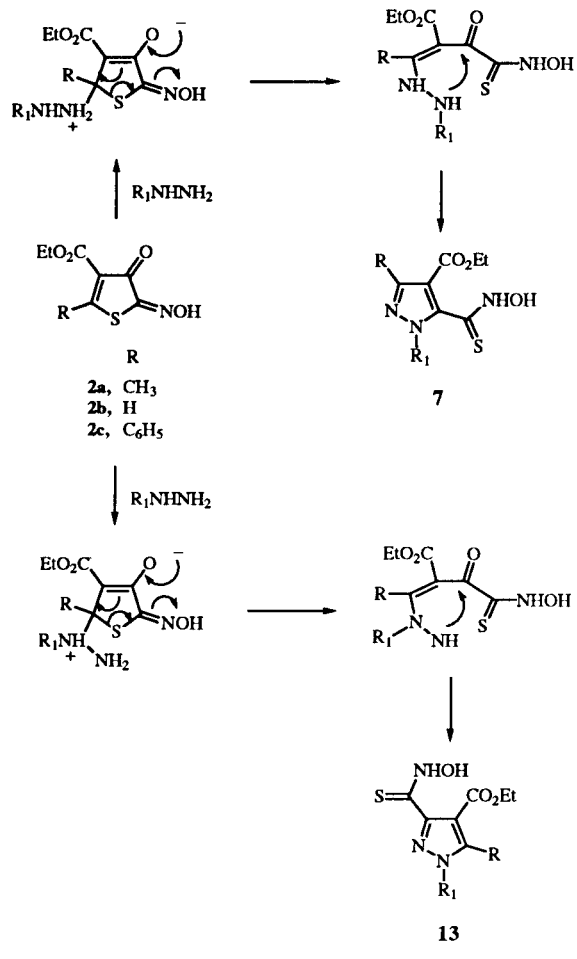


An authentic sample of the product derived from reaction of the Benary intermediate with sodium methoxide and methyl iodide was prepared by reaction of **11** with *N*-chlorosuccinimide followed by treatment with sodium methanethiolate in methanol [15,19] (Scheme 5) and was thus identified as the *S*-methyl thiohydroxamate **12e**. It is known that thiohydroxamic acids react with methyl iodide to give *S*-alkylthiohydroxamates [20].

Reaction of **2a-c** with Substituted Hydrazines.

Because of our success in correctly predicting the regiochemistry of compound **7e** using our mechanism in Scheme 3, we decided to examine the reaction of a number of substituted hydrazines with **2a** and other 2-substituted 4-oxo-5-hydroximinothiophenes. Our working mechanism, applicable to the reaction of **2** with alkyl and aryl hydrazines, is shown in Scheme 6. Clearly, the mechanism in Scheme 6 would predict the formation of pyrazolyl-5-thiohydroxamic acids from the reaction of phenylhydrazine and *t*-butylhydrazine with **2** (terminal nitrogen most nucleophilic in these hydrazines). With methylhydrazine the α-nitrogen is most nucleophilic and the formation of pyrazolyl-3-thiohydroxamic acids would be predicted (see Scheme 6).

Scheme 6

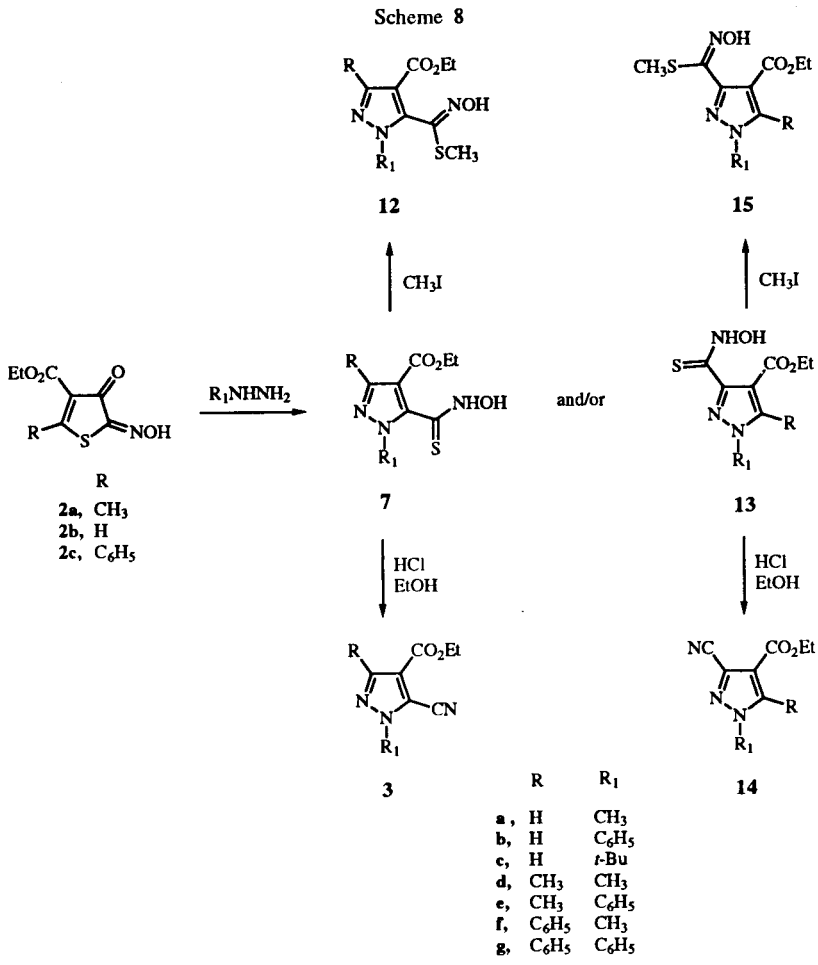


The precursor thiophenes, **8a-c**, were prepared according to literature methods [12,21-24]. Nitrosation of **8a-c** with isoamyl nitrite in ethanol (Scheme 7) gave **2a-c** [7].

Scheme 7

The oxime analogs **2a-c** were reacted with methylhydrazine, phenylhydrazine, and *t*-butylhydrazine in acetic acid to give the thiohydroxamic acid products **7** or **13** as shown in Scheme 8 and Table 1. The yields in Table 1 are for the products isolated by filtration of the reaction mixtures after quenching with water. In all except the single case noted in the table, the products were single isomers and required no further purification.

Scheme 8



The 3(5)-pyrazolylthiohydroxamic acids **7** and **13** were converted to the corresponding cyanopyrazoles **3** and **14**, respectively, when exposed to hydrochloric acid in ethanol (Scheme 8). Compounds **7g** and **13a** were also reacted with methyl iodide and sodium methoxide [20] to give **12g** and **15a**, respectively (Scheme 8).

Compounds **2a-c** were also reacted with hydrazine, yielding the expected 3(5)-pyrazolethiohydroxamic acids **16a-c** shown in Scheme 9. Compounds **16a-c** gave cyanopyrazoles **17a-c** when exposed to hydrochloric acid in ethanol. Compounds **17a** and **17c** could be converted to **18a** and **18b**, respectively, by reaction with potassium hydroxide in ethanol.

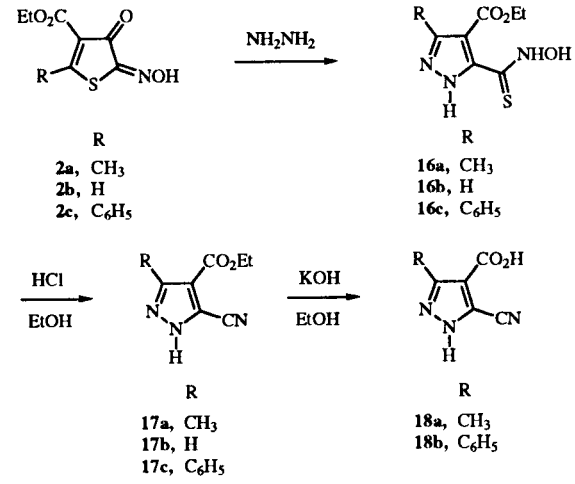
Table I

Yield Data for the Preparation of **7** and **13**

Substrate	R	R_1	Product	Yield (%)
2a	CH_3	CH_3	**13d**	44
2a	CH_3	C_6H_5	**7e**	85
2b	H	CH_3	**13a**	70
2b	H	C_6H_5	**13b**	79
2b	H	t-C_4H_9	**13c**	76
2c	C_6H_5	CH_3	**13f**	96 [a]
2c	C_6H_5	C_6H_5	**7g**	94

[a] Compound **13f** is contaminated by 10% **7f**. All other yields are of unrecrystallized pure products.

Scheme 9



Mechanism and Regiochemistry.

Scheme 8 and Table I summarize the pyrazole-3- and 5-thiohydroxamic acids prepared by the reaction of oxominothiophenes **2** with substituted hydrazines. The reactions of methylhydrazine with the three hydroximinothiophenes **2a-c** produce the corresponding pyrazole-3-thiohydroxamic acids **13d, 13a, 13f**, respectively. This is consistent with the conjugate addition mechanism proposed in Scheme 6 when the α-nitrogen of methylhydrazine is the most nucleophilic [25,26].

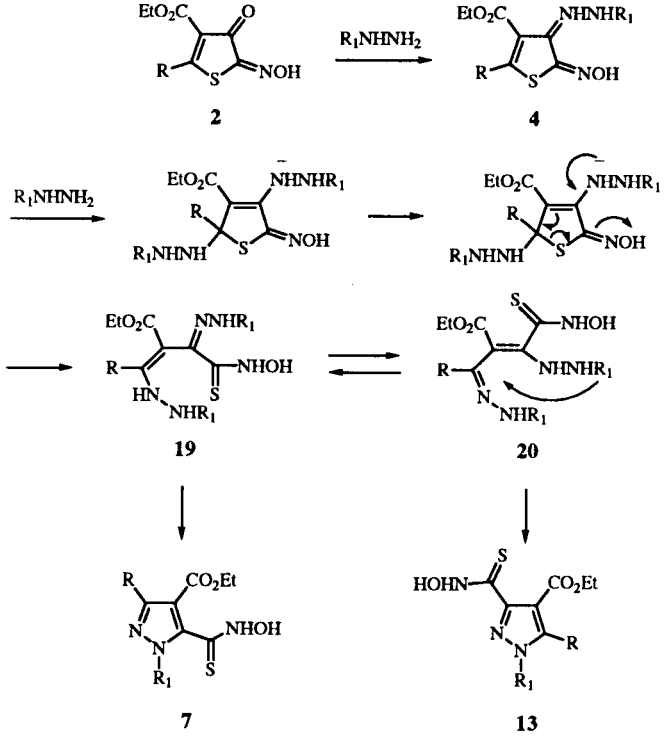
The fact that the reactions of phenylhydrazine with **2a** and **2c** produce 5-pyrazolylthiohydroxamic acid regioisomers **7e** and **7g** is also consistent with the conjugate addition of the more nucleophilic terminal nitrogen of phenylhydrazine (Schemes 6, 8 and Table 1).

In two cases, reaction of **2b** with phenylhydrazine and *t*-butylhydrazine, the isolated thiohydroxamic acids were the pyrazolyl-3-thiohydroxamic acids **13b** and **13c** and not the 5-isomers predicted by conjugate addition of what is generally considered to be the more nucleophilic terminal nitrogen of phenylhydrazine or *t*-butylhydrazine [26].

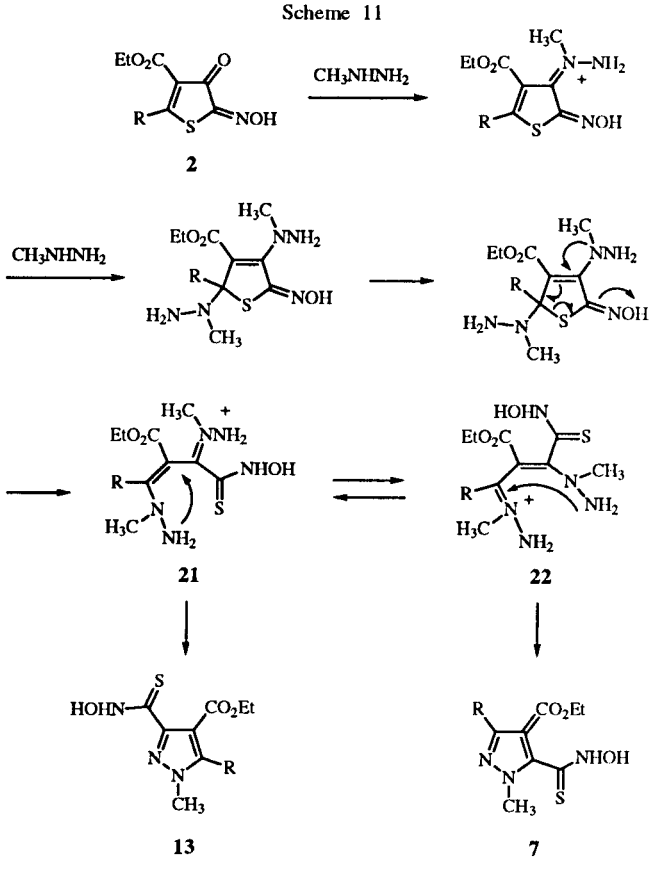
Due to the two exceptional cases in which the correct regioisomer is not correctly predicted by the mechanism illustrated in Scheme 6, we sought a mechanistic rationale which could explain all of the regiochemical outcomes of our experiments. Although the new mechanism we arrived at (Scheme 10) is not very useful as a predictive tool, we believe it can be used to explain all the results summarized in Table 1. For example, in the two cases which are not predicted by the mechanism in Scheme 6, **13b** from **2b** and **13c** from **2b**, Scheme 10 can be used to rationalize the formation of **13b** and **13c**. Thus, formation of the hydrazone **4** followed by conjugate addition of a second mole of substituted hydrazine might give the tautomers **19** and **20**. If R = methyl or phenyl and R_1 = phenyl or *t*-butyl, we know that pyrazole isomer **7** is formed. This would mean that either **19** is favored over **20** in this case or the rate of cyclization of **19** to **7** is faster than the rate of cyclization of **20** to **13**. If R = H and R_1 = phenyl or *t*-butyl, **13** is produced leading to the conclusion that in this case either **20** is favored over **19** or the rate of cyclization of **20** to **13** is faster than the rate of cyclization of **19** to **7**.

Although the products obtained from conjugate addition of methylhydrazine are correctly predicted by Scheme 6, a mechanism similar to Scheme 10 can be considered for the reaction of methylhydrazine with **2** (Scheme 11). In this case, intermediate **21** would apparently be favored or would cyclize faster in all cases where R = H, methyl, or phenyl since the 3-pyrazolylthiohydroxamic acids **13** are formed. Intermediates such

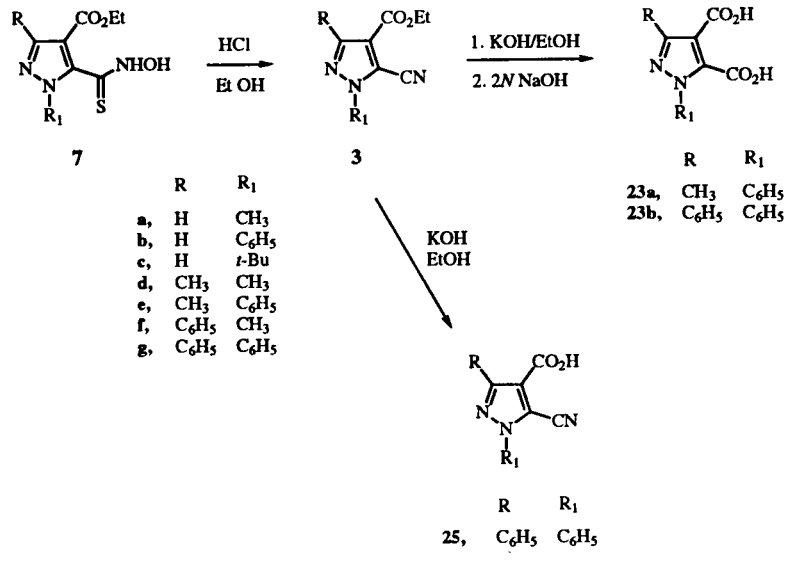
Scheme 10



Scheme 11



Scheme 12



7

	R	R_1
a,	H	CH_3
b,	H	C_6H_5
c,	H	*t*-Bu
d,	CH_3	CH_3
e,	CH_3	C_6H_5
f,	C_6H_5	CH_3
g,	C_6H_5	C_6H_5

3

	R	R_1
23a,	CH_3	C_6H_5
23b,	C_6H_5	C_6H_5

	R	R_1
25,	C_6H_5	C_6H_5

as **19**, **20**, and **21** and **22** have been proposed in the conversion of pyrones to pyrazoles [27].

It might be expected that a mixture of 3- and 5-thiohydroxamic acids could result from reaction of **2** with many of the *N*-substituted hydrazines, since mixtures of pyrazole isomers are frequently observed in preparations of pyrazoles from substituted hydrazines [28]. In only one of the cases we have studied (**13f** contained 10% of **7f** -see discussion below), did we isolate by filtration a mixture of isomeric thiohydroxamic acids. Instead, we found that the minor isomers were formed in some cases but were to be found in the filtrates.

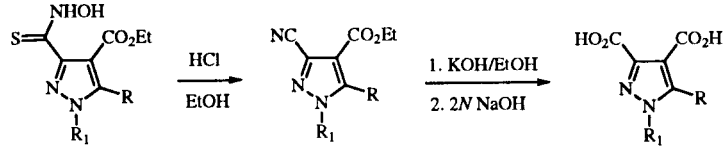
In order to examine the filtrates from the isolation of **7** or **13**, we first converted any thiohydroxamic acids in the filtrates to the corresponding nitriles by reaction with hydrochloric acid in ethanol at reflux. This was done because the nitriles are more stable to the flash chromatographic and capillary gas chromatographic conditions required to separate the isomers. Using these methods we found that the filtrate from isolation of **13b** contains exclusively the isomer **7b** (Scheme 8). The filtrate from isolation of **13f** contained a 50:50 mixture of isomers **7f** and **13f**. The filtrates from isolation of **7g** and **13a** contained only residual **7g** and **13a**, respectively, and none of the isomeric thiohydroxamic acids.

In summary, it is possible to explain all of our results except for the formation of **13b** and **13c** from **2b** by Scheme 6. It is also possible to rationalize our results by the alternative mechanisms shown in Schemes 10 and 11. While we have not isolated any hydrazones such as **4** and the mechanism shown in Scheme 6 explains most of our results, we believe a mechanism involving initial formation of a hydrazone may be operative at least in some of the cases studied.

Structural Assignments.

In some of the cases positional assignments of the substituents on the pyrazole ring were made by conversion of the 3- or 5-pyrazolethiohydroxamic acids **7** or **13** to the corresponding 3- or 5-cyanopyrazoles **3** or **14** or the 3,4- or 4,5-pyrazoledicarboxylic acids **23** or **24** (Schemes 12 and 13) which were known in the literature. Conversion of **7** or

Scheme 13



13

	R	R_1
a,	H	CH_3
b,	H	C_6H_5
c,	H	*t*-Bu
d,	CH_3	CH_3
e,	CH_3	C_6H_5
f,	C_6H_5	CH_3
g,	C_6H_5	C_6H_5

14

	R	R_1
24a,	CH_3	CH_3
24b,	H	*t*-Bu
24c,	H	CH_3
24d,	H	C_6H_5
24e,	C_6H_5	CH_3

Table 2

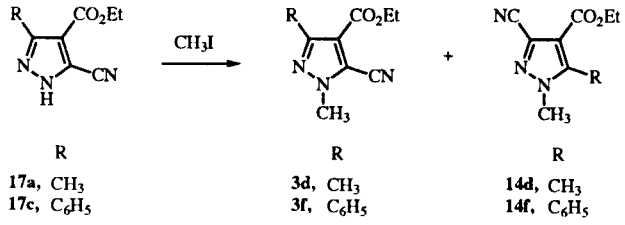
Melting Point Data tor Cyanopyrazoles **3**, **14**, **17**, **18**, **25** and Diacids **23** and **24**

No.	mp °C	mp °C [lit]	No.	mp °C	mp °C [lit]
3e	84-86	88-89 [7]	**18a**	271-272	
3g	113-114		**18b**	209-211	
3d	79-81		**23a**	197-198	195-198 [29]
3f	51-52		**23b**	197-199	197 [32,33]
14d	133-135		**24a**	256-257	
14c	oil	oil [30]	**24c**	236-237	239-241 [34-36]
14a	90-91	91-93 [3,31]	**24d**	227-230	232 [37]
14b	110-112		**25**	204-207	
14f	103-104				
17a	174-177				
17b	149-151	148-150 [30]			
17c	150-151				

13 to **3** or **14** was accomplished by reaction with catalytic hydrochloric acid in ethanol. The dicarboxylic acids **23** or **24** were prepared by reaction of **3** or **14** with potassium hydroxide in ethanol followed by 2*N* sodium hydroxide solution [7,29]. Cyanoacid **25** was prepared by reaction of **3g** with hot ethanolic potassium hydroxide (Scheme 12). Data for all of the derivatives is collected in Table 2. Two other nitriles, **3d** and **3f**, prepared according to Scheme 14, are also included in the table for completeness.

The structures of **14d** and **14f** and their corresponding diacids **24a** and **24e** (Scheme 13) were unknown in the literature. These compounds were identified by preparation of a mixture of the 3- and 5-cyano compounds by *N*-methylation of the *N*-desmethyl analogs **17a** and **17c** (Scheme 14). The 5-cyano analogs **3d** and **3f** were then prepared unambiguously to allow structural assignment of both isomers. Thus, methylation of **17a** with methyl iodide [38] gave both ethyl 3-cyano-1,5-dimethyl-1*H*-pyrazole-4-carboxylate **14d** and ethyl 5-cyano-1,3-dimethyl-1*H*-pyrazole-4-carboxylate **3d** (Scheme 14), which were readily separated by flash chromatography. Similarly, a mixture of isomers of **14f** and **3f** was prepared by methylation of **17c** and the isomers were separated.

Scheme 14



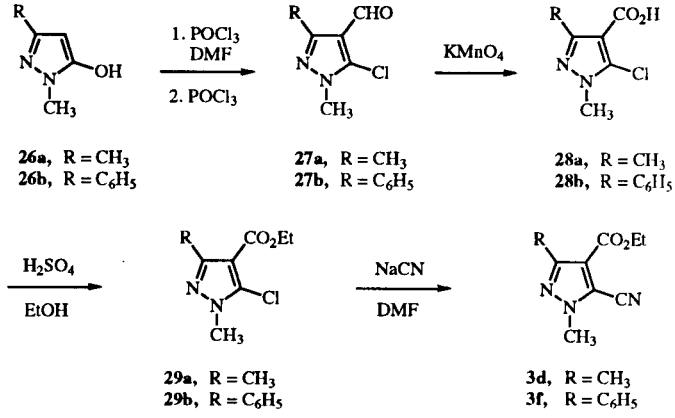
R R R

17a, CH_3 **3d**, CH_3 **14d**, CH_3

17c, C_6H_5 **3f**, C_6H_5 **14f**, C_6H_5

Authentic samples of the 5-cyano isomers **3d** and **3f** were prepared unambiguously as described below (Scheme 15). The 1,3-dimethyl-5-cyano analog **3d** was prepared by reaction of ethyl 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carboxylate **29a** [1] with sodium cyanide in dimethyl formamide. The 1-methyl-3-phenyl-5-cyano analog **3f** was prepared similarly by preparation of the 5-chloropyrazole **29b** from **26b** [39] and subsequent reaction of **29b** with sodium cyanide. Thus, with authentic samples of 5-cyano isomers **3d** and **3f** in hand, **14d** and **14f** were identified as the 3-cyano isomers. This also established **13d** and **13f** as the products of the reaction of methylhydrazine with **2a** and **2c**, respectively (Scheme 8 and Table 1).

Scheme 15



26a, $R = CH_3$ **27a**, $R = CH_3$ **28a**, $R = CH_3$

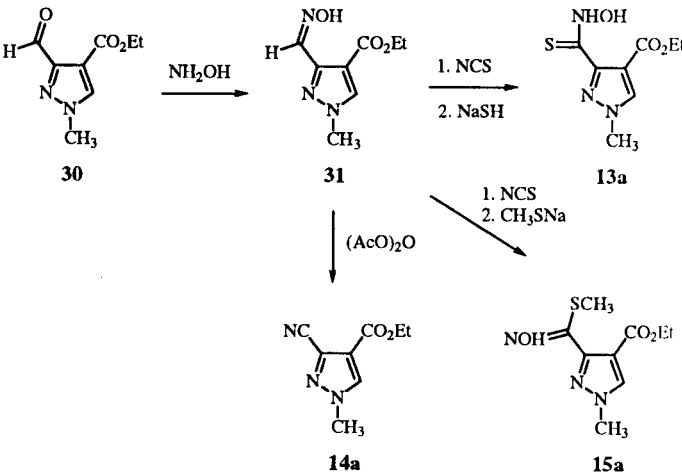
26b, $R = C_6H_5$ **27b**, $R = C_6H_5$ **28b**, $R = C_6H_5$

29a, $R = CH_3$ **3d**, $R = CH_3$

29b, $R = C_6H_5$ **3f**, $R = C_6H_5$

In addition to the synthesis of **7e** described above, three authentic thiohydroxamic acid analogs were prepared (Schemes 16 and 17). Reaction of hydroxylamine with **30** [38] gave the corresponding oxime **31** (Scheme 16). Reaction of **31** with *N*-chlorosuccinimide followed by sodium hydrosulfide [18, 41-43] gave an authentic sample of the 3-pyrazolethiohydroxamic acid **13a**, identical to **13a** prepared by the method of Benary and Silberstrom [7]. Compound **31** could also be converted to **15a** using *N*-chlorosuccinimide and sodium methanethiolate. Compound **15a** prepared from **31** was identical to **15a** prepared from **13a** (Scheme 8).

Scheme 16

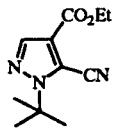


30 **31** **13a**

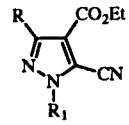
14a **15a**

Table 3

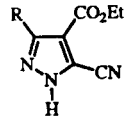
^{13}C Assignments for Compounds **1**, **3**, **14**, and **17**



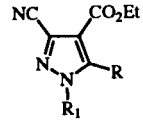
1



	R	R_1
3d	CH_3	CH_3
3e	CH_3	C_6H_5
3f	C_6H_5	CH_3
3g	C_6H_5	C_6H_5



	R
17a	CH_3
17b	H
17c	C_6H_5



	R	R_1
14a	H	CH_3
14b	H	C_6H_5
14c	H	*t*-Bu
14d	CH_3	CH_3
14f	C_6H_5	CH_3

No.	C-3	C-4	C-5	CN	Ethyl Ester	Other Carbon Atoms
1	139.6	114.4	122.7	111.4	14.7, 61.7, 161.1	29.9 (Me-C), 64.9 (C-N)
3d	149.9	116.3	117.6	109.7	13.8, 60.6, 160.7	12.9 (Me-C), 39.6 (Me-N)
3e	152.3	119.5	117.6	110.8	14.7, 61.8, 161.5	14.0 (Me-C), 124.7, 130.5, 130.7, 138.4 (Ph-N)
3f	153.2	116.9	119.4	109.6	13.9, 61.4, 160.7	38.9 (Me-N), 128.1, 129.3, 129.3, 130.7 (Ph-C)
3g	154.5	119.9	119.1	111.6	15.4, 62.9, 161.9	125.9, 129.7, 131.0, 131.4, 131.8, 132.0 (Ph)
14a	124.1	117.4	136.1	112.7	13.9, 60.7, 159.9	39.6 (Me-N)
14b	126.4	119.7	133.6	112.9	14.6, 61.6, 160.4	120.4, 129.4, 130.3, 138.6 (Ph-N)
14c	124.2	117.8	134.1	113.5	14.6, 61.3, 160.7	29.4 (Me-C), 62.4 (C-N)
14d	124.3	114.8	145.7	113.8	14.6, 61.2, 161.4	11.1 (Me-C), 38.2 (Me-N)
14f	124.4	115.3	146.6	112.9	13.5, 60.4, 159.9	38.4 (Me-N), 126.9, 128.3, 129.9, 130.1 (Ph-C)
17a	146.1	114.6	126.6	114.4	15.0, 61.4, 162.1	11.7 (Me-C)
17b	134.1	117.1	124.8	113.1	14.0, 60.6, 160.4	
17c	146.4	126.7	126.5	113.2	13.6, 60.6, 160.4	128.2, 129.5, 130.0 (Ph-C)

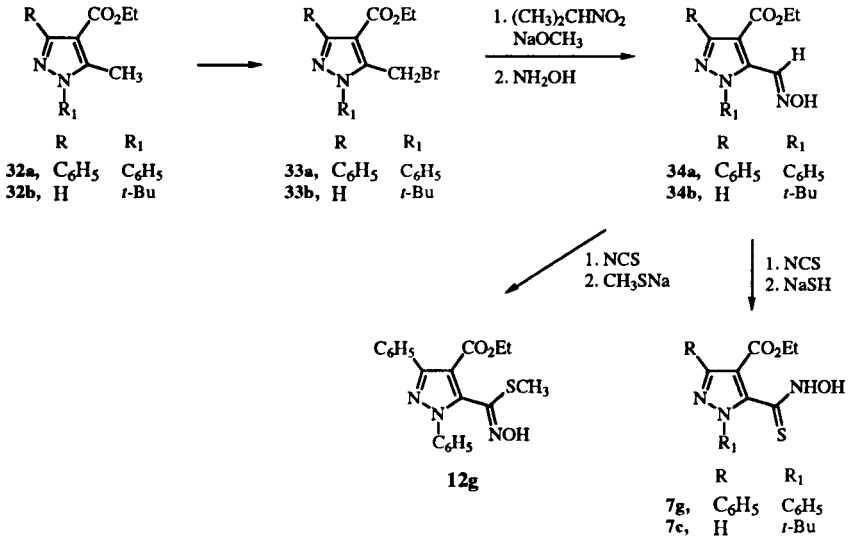
The 1,3-diphenylpyrazole-5-thiohydroxamic acid analog **7g** was prepared from ethyl 1,3-diphenyl-5-methyl-(1*H*)-pyrazole-4-carboxylate **32a** [32] (Scheme 17). Thus, **32a** was brominated using 1,3-dibromo-5,5-dimethylhydantion to give **33a**. Compound **33a** was oxidized with 2-nitropropane [43] to give the corresponding aldehyde, which was not isolated but reacted with hydroxylamine to give the oxime **34a**. Compound **34a** was reacted with *N*-chlorosuccinimide followed by sodium hydrosulfide to give **7g**. Compound **7g** thus prepared was identical to **7g** prepared by the reaction of **2c** and phenylhydrazine by the method of Benary and Silberstrom [7]. In a similar fashion to the preparation of **12e** from **11** (Scheme 5) described earlier, **34a** was converted to **12g** (Scheme 17).

Compound **7c**, the 5-pyrazolethiohydroxamic acid isomer of compound **13c**, described earlier, was prepared similarly from 1-(1,1-dimethylethyl)-5-methyl-(1*H*)-pyrazole-4-carboxylate **34b** [43] by the method shown in Scheme 17.

The position of the substituents on the pyrazole ring of the 3- or 5-unsubstituted cyanopyrazoles was corroborated using proton nmr data [44,45]. Thus, Beck reported a downfield C-5 proton shift of 0.58-0.75 ppm for the 3-cyano-5-unsubstituted pyrazoles when the spectra in deuteriodimethyl sulfoxide were compared to the spectra run in deuteriochloroform [3,46,47,25]. The nmr spectra of compounds **14a-c** (Scheme 8) show a similar downfield shift of 0.58-0.85 ppm when run in deuteriodimethyl sulfoxide compared to deuteriochloroform, and were, therefore, assigned the 3-cyano structure.

The structures of the *N*-substituted regioisomeric pyrazoles were confirmed by long range HETCOR experiments [48] and by ^{13}C nmr spectroscopy (see Table 3) [11,49-51].

Scheme 17



In summary, we have shown that the reactions of alkyl and aryl hydrazines with **2** give 3- or 5-thiohydroxamic acids **7** or **13** instead of the hydrazones **4** previously described by Benary and Silberstrom. Two alternate mechanisms have been proposed which account for the observed regiochemistry.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance studies were performed on a General Electric QE-300 spectrometer. The mass spectra, infrared spectra, and the elemental analyses were performed by Molecular Structure Research at Eli Lilly and Co. Merck silica gel 60 F254 plates (0.25mm) were used for thin layer chromatography. Merck silica gel 60 (230-400 mesh) was employed for flash column chromatography.

4-Hydroxy-3-thiophenecarboxylic Acid, Ethyl Esters.

The thiophenes used in this study (4-hydroxy-2-methyl-3-thiophenecarboxylic acid, ethyl ester **8a** [12,21], 4-hydroxy-3-thiophenecarboxylic acid, ethyl ester **8b** [23], and 4-hydroxy-2-phenyl-3-thiophenecarboxylic acid, ethyl ester **8c** [12]) were prepared by literature methods and gave physical constants consistent with literature values.

General Procedure for the Preparation of 4,5-Dihydro-5-(hydroxyimino)-4-oxo-3-thiophenecarboxylic Acid, Ethyl Esters **2** [7].

To a solution of the 4-hydroxyl-3-thiophenecarboxylic acid, ethyl ester **8a**, **8b**, or **8c** (100 mmoles) in ethanol (27 ml) at 50° was added dropwise over 10 minutes isoamyl nitrite (23.43 g, 200 mmoles). The reaction mixture was stirred at 50° for 1 hour. A precipitate formed upon cooling the reaction to 0°. The precipitate was either collected by filtration and recrystallized from ethanol, concentrated to dryness and purified by flash chromatography (hexane/ethyl acetate), or diluted with hexane and filtered. The following compounds were prepared by this method:

4,5-Dihydro-5-(hydroxyimino)-2-methyl-4-oxo-3-thiophenecarboxylic Acid, Ethyl Ester (**2a**).

This compound was obtained from **8a** as green needles in 75% yield after trituration with hexane and filtration, mp 158° (lit [7] mp 110-130°); ^1H nmr (deuteriodimethyl sulfoxide): δ 1.24 (3H, CH_3, t), 2.64 (3H, CH_3, s), 4.21 (2H, CH_2, q), 13.84 (1H, NOH, broad).

Anal. Calcd. for $C_8H_9NO_4S$: C, 44.65; H, 4.21; N, 6.51; S, 14.90. Found: C, 44.38; H, 4.30; N, 6.73; S, 14.70.

4,5-Dihydro-5-(hydroxyimino)-4-oxo-3-thiophenecarboxylic Acid, Ethyl Ester (**2b**).

This compound was obtained from **8b** as a yellow powder in 34% yield after recrystallization from ethanol, mp 150-152°; ^1H nmr (deuteriodimethyl sulfoxide): δ 1.23 (3H, CH_3, t), 4.18 (2H, CH_2, q), 9.39 (1H, CH, s), 14.00 (1H, NOH, s).

Anal. Calcd. for $C_7H_7NO_4S$: C, 41.79; H, 3.51; N, 6.96; S, 15.93. Found: C, 41.49; H, 3.49; N, 6.68; S, 15.83.

4,5-Dihydro-5-(hydroxyimino)-4-oxo-2-phenyl-3-thiophenecarboxylic Acid, Ethyl Ester (**2c**).

This compound was obtained from **8c** as yellow needles in 90% yield after flash chromatography using hexane/ethyl acetate (1:1), mp 133-135°; ^1H nmr (deuteriodimethyl sulfoxide): δ 1.07 (3H, CH_3, t), 4.15 (2H, CH_2, q), 7.58 (5H, ArH, m), 14.09 (1H, NOH, broad).

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 3.99; N, 5.05. Found: C, 56.38; H, 4.07; N, 5.05.

General Procedure for the Preparation of 5-(*N*-Hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters (**7**), 3-(*N*-Hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters (**13**), and 3-*N*-Hydroxyaminothiocarbonyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters (**16**) from **2**.

To a solution of the 4,5-dihydro-5-(hydroxyimino)-4-oxo-3-thiophenecarboxylic acid, ethyl ester **2a**, **2b**, or **2c** (100 mmoles) in acetic acid (200 ml) at ambient temperature was added drop-

wise over 5 minutes the desired hydrazine (110 mmoles). The reaction mixture was stirred for 2 hours at ambient temperature. The reaction was diluted with water (200 ml) and the precipitate was filtered. The following compounds were obtained by this method:

5-(*N*-Hydroxyaminothiocarbonyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7e**).

This compound was obtained from **2a** and phenylhydrazine as a tan powder in 83% yield, mp 158-159°; ^{1}H nmr (deuteriochloroform): δ 1.39 (3H, CH_3, t), 2.53 (3H, CH_3, s), 4.39 (2H, CH_2, q), 7.43 (5H, ArH, s), 8.5 (1H, OH, broad); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.20 (3H, CH_3, t), 2.40 (3H, CH_3, s), 4.15 (2H, CH_2, q), 7.43 (5H, ArH, m), 10.60 (1H, OH, broad), 13.60 (1H, NH, broad).

Anal. Calcd. for $C_{14}H_{14}N_3O_3S$: C, 55.25; H, 4.64; N, 13.81; S, 10.53. Found: C, 55.36; H, 4.82; N, 13.94; S, 10.76.

1,3-Diphenyl-5-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7g**).

This compound was obtained from **2c** and phenylhydrazine as yellow needles in 94% yield, mp 159-160°; ^{1}H nmr (deuteriochloroform): δ 1.16 (3H, CH_3, t), 4.23 (2H, CH_2, q), 7.53 (10H, ArH, m); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.14 (3H, CH_3, t), 4.12 (2H, CH_2, q), 7.51 (10H, ArH, m), 10.7 (1H, OH, broad), 13.7 (1H, NH, broad).

Anal. Calcd. for $C_{19}H_{17}N_3O_3S$: C, 62.11; H, 4.66; N, 11.44; S, 8.73. Found: C, 61.89; H, 4.71; N, 11.18; S, 8.95.

3-(*N*-Hydroxyaminothiocarbonyl)-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**13a**).

This compound was obtained from **2b** and methylhydrazine as fine yellow crystals in 72% yield, mp 137-141; ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, CH_3, t), 4.05 (3H, CH3, s), 4.38 (2H, CH_2, q), 8.05 (1H, CH, s), 10.25 (1H, OH, d), 15.10 (1H, NH, s); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.20 (3H, CH_3, t), 3.85 (3H, CH_3, s), 4.13 (2H, CH_2, q), 8.28 (1H, CH, s), 10.17 (1H, OH, broad), 13.4 (1H, NH, broad).

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.91; H, 4.92; N, 18.33.

3-(*N*-Hydroxyaminothiocarbonyl)-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**13b**).

This compound was obtained from **2b** and phenylhydrazine as a white powder in 79% yield, mp 161-165°; ^{1}H nmr (deuteriochloroform): δ 1.45 (3H, CH_3, t), 4.45 (2H, CH_2, q), 7.48 (3H, ArH, m), 7.81 (2H, ArH, m), 8.54 (1H, CH, s), 10.37 (1H, OH, broad); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.27 (3H, CH_3, t), 4.26 (2H, CH_2, q), 7.41 (3H, ArH, m), 7.91 (2H, ArH, d), 9.00 (1H, CH, s), 10.34 (1H, OH, broad), 13.40 (1H, NH, broad).

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.12; S, 11.00. Found: C, 53.57; H, 4.41; N, 14.28; S, 11.18.

1-(1,1-Dimethylethyl)-3-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**13c**).

This compound was obtained from **2b** and *t*-butylhydrazine as a white powder in 76% yield, mp 169-172°; ^{1}H nmr (deuteriochloroform): δ 1.41 (3H, CH_3, t), 1.68 (9H, *t*-butyl, s), 4.39 (2H, CH_2, q), 8.13 (1H, CH, s); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.21 (3H, CH_3, t), 1.52 (9H, *t*-butyl, s), 4.14 (2H, CH_2, q), 8.31 (1H, CH, s), 10.16 (1H, OH, Broad), 13.36 (1H, NH, broad).

Anal. Calcd. for $C_{11}H_{17}N_3O_3S$: C, 48.69; H, 6.31; N, 15.49; S, 11.82. Found: C, 48.86; H, 6.44; N, 15.51; S, 11.95.

1,5-Dimethyl-3-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**13d**).

This compound was obtained from **2a** and methylhydrazine as a tan powder in 52% yield, mp 156-157°; ^{1}H nmr (deuteriochloroform): δ 1.43 (3H, CH_3, t), 2.56 (3H, CH_3, s), 3.95 (3H, CH_3, s), 4.42 (2H, CH_2, q), 10.32 (1H, OH, broad); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.18 (3H, CH_3, t), 2.43 (3H, CH_3, s), 3.75 (3H, CH_3, s), 4.10 (2H, CH_2, q), 10.1 (1H, OH, broad), 13.35 (1H, NH, broad).

Anal. Calcd. for $C_9H_{12}N_3O_3S$: C, 44.62; H, 4.99; N, 17.34; S, 13.23. Found: C, 44.55; H, 5.05; N, 17.46; S, 12.95.

3-(*N*-Hydroxyaminothiocarbonyl)-1-methyl-5-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**13f**).

This compound was obtained from **2c** and methylhydrazine as an orange powder in 96% yield, mp 125-128°; ^{1}H nmr (deuteriochloroform): δ 0.82 (3H, CH_3, t), 3.78 (3H, CH_3, s), 4.04 (2H, CH_2, q), 7.40 (10H, ArH, m), 10.3 (1H, OH, broad); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 0.98 (3H, CH_3, t), 3.68 (3H, CH_3, s), 3.96 (2H, CH_2, q), 7.45 (5H, ArH, m), 10.25 (1H, OH, broad), 13.45 (1H, NH, broad).

Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76. Found: C, 55.00; H, 5.00; N, 14.06.

3-(*N*-Hydroxyaminothiocarbonyl)-5-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**16a**).

This compound was obtained from **2a** and hydrazine as a tan powder in 91% yield, mp 166-167°; ^{1}H nmr (deuteriochloroform): δ 1.45 (3H, CH_3, t), 2.53 (3H, CH_3, s), 4.44 (2H, CH_2, q), 9.66 (1H, OH, broad), 11.35 (1H, NH, broad); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.20 (3H, CH_3, t), 2.38 (3H, CH_3, s), 3.33 (1H, NH, broad), 4.12 (2H, CH_2, q), 10.1 (1H, OH, broad), 13.4 (1H, NH, broad).

Anal. Calcd. for $C_9H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33; S, 13.98. Found: C, 41.99; H, 4.95; N, 18.40; S, 14.13.

3-(*N*-Hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**16b**).

This compound was obtained from **2b** and hydrazine as yellow needles in 85% yield, mp 145-147°; ^{1}H nmr (deuteriochloroform): δ 1.44 (3H, CH_3, t), 4.44 (2H, CH_2, q), 8.13 (1H, CH, s), 9.7 (1H, OH, broad), 11.35 (1H, NH, broad), 15.23 (1H, NH, broad); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.22 (3H, CH_3, t), 3.38 (1H, NH, broad), 4.16 (2H, CH_2, q), 8.3 (1H, CH, broad), 10.25 (1H, OH, broad), 13.44 (1H, NH, broad).

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.52; S, 14.90. Found: C, 39.14; H, 4.07; N, 19.68; S, 15.01.

3-(*N*-Hydroxyaminothiocarbonyl)-5-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**16c**).

This compound was obtained from **2c** and hydrazine as yellow needles in 91% yield, mp 136-138°; ^{1}H nmr (deuteriochloroform): δ 1.06 (3H, CH_3, t), 4.22 (2H, CH_2, q), 7.46 (5H, ArH, m), 9.7 (1H, OH, broad), 11.5 (1H, NH, broad); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.12 (3H, CH_3, t), 4.08 (2H, CH_2, q), 7.53 (5H, ArH, m), 10.25 (1H, OH, broad), 13.6 (1H, NH, broad).

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42; S, 11.00. Found: C, 53.56; H, 4.59; N, 14.34; S, 11.12.

General Procedure for the Preparation of 3-Cyano-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters and 5-Cyano-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters from **7**, **13** and **16**.

To a suspension of the (*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic acid, ethyl ester **7**, **13**, or **16** (2 mmoles) in ethanol (20 ml) was added 2 drops of concentrated hydrochloric acid. The reaction mixture was heated for 6 hours at reflux. The reaction was concentrated to dryness and purified by recrystallization from water, ethanol, ethyl acetate, or purified by flash chromatography (hexane/ethyl acetate).

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

This compound was obtained from **7e** as white needles in 80% yield after flash chromatography using hexane/ethyl acetate, mp 84-86° (lit [7] mp 88-89°). ^{1}H nmr (deuteriochloroform): δ 1.43 (3H, CH_3, t), 2.59 (3H, CH_3, s), 4.42 (2H, CH_2, q), 7.53 (3H, ArH, m), 7.70 (2H, ArH, m).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.14; H, 5.30; N, 16.69.

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

This compound was obtained from **7g** as white needles in 45% yield after recrystallization from ethanol, mp 113-114°; ^{1}H nmr (deuteriochloroform): δ 1.38 (3H, CH_3, t), 4.40 (2H, CH_2, q), 7.6 (10H, ArH, m); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.26 (3H, CH_3, t), 4.31 (2H, CH_2, q), 7.6 (10H, ArH, m).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 72.17; H, 4.74; N, 13.48.

3-Cyano-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14a**).

This compound was obtained from **13a** as a tan powder in 58% yield after recrystallization from water, mp 90-91° (lit [3] mp 91-93° and [31] mp 90°); ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, CH_3, t), 4.00 (3H, CH_3, s), 4.35 (2H, CH_2, q), 7.95 (1H, CH, s); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.25 (3H, CH_3, t), 3.95 (3H, CH_3, s), 4.25 (2H, CH_2, q), 8.55 (1H, CH, s).

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.90; H, 5.08; N, 23.73.

3-Cyano-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14b**).

This compound was obtained from **13b** as white needles in 66% yield after recrystallization from ethanol, mp 110-112°; ^{1}H nmr (deuteriochloroform): δ 1.45 (3H, CH_3, t), 4.43 (2H, CH_2, q), 7.05 (3H, ArH, m), 7.73 (2H, ArH, d), 8.50 (1H, CH, s); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.32 (3H, CH_3, t), 4.30 (2H, CH_2, q), 7.50 (3H, ArH, m), 7.95 (2H, ArH, d), 9.35 (1H, CH, s).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.49; H, 4.63; N, 17.50.

3-Cyano-1-(1,1-dimethylethyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14c**).

This compound was obtained from **13c** as an oil in 100% yield after flash chromatography using hexane/ethyl acetate (4:1) (lit [30]); ^{1}H nmr (deuteriochloroform): δ 1.38 (3H, CH_3, t), 1.62 (9H, *t*-butyl, s), 4.37 (2H, CH_2, q), 8.07 (1H, CH, s); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.25 (3H, CH_3, t), 1.58 (9H, *t*-butyl, s), 4.30 (2H, CH_2, q), 8.65 (1H, CH, s).

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.89. Found: C, 59.67; H, 6.94; N, 19.19.

3-Cyano-1,5-dimethyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14d**).

This compound was obtained from **13d** as gray needles in 74% yield after recrystallization from ethanol, mp 133-135°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.28 (3H, CH_3, t), 2.51 (3H, CH_3, s), 3.85 (3H, CH_3, s), 4.26 (2H, CH_2, q).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.12; H, 5.78; N, 21.83.

3-Cyano-1-methyl-5-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14f**).

This compound was obtained from **13f** as white crystals in 52% yield after flash chromatography using hexane/ethyl acetate (2:1), mp 103-104°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.08 (3H, CH_3, t), 3.78 (3H, CH_3, s), 4.12 (2H, CH_2, q), 7.54 (5H, ArH, m).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.97; H, 5.29; N, 16.58.

3-Cyano-5-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**17a**).

This compound was obtained from **16a** as white crystals in 83% yield after recrystallization from ethyl acetate, mp 174-177°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.33 (3H, CH_3, t), 2.50 (3H, CH_3, s), 4.29 (2H, CH_2, q).

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.75; H, 5.14; N, 23.47.

3-Cyano-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**17b**).

This compound was obtained from **16b** as fine white crystals in 59% yield after recrystallization from water, mp 149-151° (lit [30] mp 148-150°); ^{1}H nmr (deuteriochloroform): δ 1.43 (3H, CH_3, t), 1.63 (1H, NH, s), 4.40 (2H, CH_2, q), 8.20 (1H, CH, s), 10.95 (1H, NH, s); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.27 (3H, CH_3, t), 4.23 (2H, CH_2, q), 8.60 (1H, CH, s).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.83; H, 4.30; N, 25.36.

3-Cyano-5-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**17c**).

This compound was obtained from **16c** as a white powder in 90% yield after flash chromatography using hexane/ethyl acetate (2:1), mp 150-151°; ^{1}H nmr (deuteriochloroform): δ 1.32 (3H, CH_3, t), 4.30 (2H, CH_2, q), 7.55 (5H, ArH, m), 11.70 (1H, NH, s); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.23 (3H, CH_3, t), 4.24 (2H, CH_2, q), 7.65 (5H, ArH, m).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.62; H, 4.64; N, 17.54.

General Procedure for the Preparation of 3- and 5-Cyano-1*H*-Pyrazole-4-carboxylic Acids **18a**, **18b**, and **25** from **17a**, **17c**, and **3g**, respectively.

A solution of the 3-and 5-cyano-1*H*-pyrazole-4 carboxylic acid, ethyl ester **3g**, **17a**, or **17c** (1 mmole) and 85% potassium hydroxide (5 mmoles) in ethanol (20 ml) was heated for 2 hours at reflux. The reaction was concentrated to dryness. The residue was dissolved in water (20 ml) and the solution acidified to a *p*H of 1 using concentrated hydrochloric acid. The precipitate that formed was collected by filtration.

3-Cyano-5-methyl-1*H*-pyrazole-4-carboxylic Acid (**18a**).

This compound was obtained from **17a** as a white solid in 77% yield, mp 271-272°.

Anal. Calcd. for $C_6H_5N_3O_2$: C, 47.69; H, 3.34; N, 27.81. Found: C, 47.97; H, 3.42; N, 28.02.

3-Cyano-5-phenyl-1*H*-pyrazole-4-carboxylic Acid (**18b**).

This compound was obtained from **17c** as a white solid in 83% yield after recrystallization from water, mp 209-211°.

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.72; H, 3.22; N, 19.58.

5-Cyano-1,3-diphenyl-1*H*-pyrazole-4-carboxylic Acid (**25**).

This compound was obtained from **3g** as a white powder in 43% yield after recrystallization from hexane/ethyl acetate, mp 204-207°.

Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.37; H, 3.96; N, 14.26.

General Procedure for the Preparation of 1H-Pyrazole-4,5-dicarboxylic Acids **23** and 1*H*-Pyrazole-3,4-dicarboxylic Acids **24**.

A solution of the 3- or 5-cyano-1*H*-pyrazole-4-carboxylic acid, ethyl ester **3** or **14** (1 mmole) and 85% potassium hydroxide (5 mmoles) in ethanol (20 ml) was heated for 2 hours at reflux. The precipitate which formed during reflux was cooled and filtered. The precipitate was suspended in 2*N* sodium hydroxide (13 ml). During a 1.5 hour reflux the solids dissolved and gave a clear, colorless solution. The reaction was cooled and acidified to a *p*H of 1 using concentrated hydrochloric acid. The resulting precipitate was collected by filtration.

3-Methyl-1-phenyl- 1*H*-pyrazole-4,5-dicarboxylic Acid (**23a**).

This compound was obtained from **3e** as white crystals in 98% yield after recrystallization from water, mp 197-198° (lit [29] mp 195-198°).

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.74; H, 4.25; N, 11.49.

1,3-Diphenyl-1*H*-pyrazole-4,5-dicarboxylic Acid (**23b**).

This compound was obtained from **3g** as tan crystals in 28% yield after recrystallization from hexane/ethyl acetate, mp 197-199° (lit [32,33] mp 197°).

Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.06; H, 4.14; N. 9.24.

1,5-Dimethyl-1*H*-pyrazole-3,4-dicarboxylic Acid (**24a**).

This compound was obtained from **14d** as tan plates in 37% yield after recrystallization from water, mp 256-257°.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.43; H, 4.19; N, 15.17.

1-Methyl-1*H*-pyrazole-3,4-dicarboxylic Acid (**24c**).

This compound was obtained from **14a** as white plates in 3% yield after recrystallization from water, mp 236-237° (lit [34,35,36] mp 239-241°).

Anal. Calcd. for $C_6H_6N_2O_4$: C,42.36; H, 3.55; N, 16.47. Found: C, 42.16; H, 3.48; N, 16.72.

1-Phenyl-1*H*-pyrazole-3,4-dicarboxylic Acid (**24d**).

This compound was obtained from **14b** as white needles in 77% yield after recrystallization from ethyl acetate/ethanol, mp 227-230° (lit [37] mp 232°); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 7.44 (1H, ArH, t), 7.58 (2H, ArH, t), 7.95 (2H, ArH, d), 9.12 (1H, CH, s).

Anal. Calcd. for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.06. Found: C, 56.71; H, 3.56; N, 11.79.

General Procedure for the Preparation of 3- and 5-Cyano-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters **3d**, **3f**, **14d**, and **14f** from 3-Cyano-1*H*-pyrazole-4-carboxylic Acid, Ethyl Esters **17a** and **17c**.

To a solution of 3-cyano-1*H*-pyrazole-4-carboxylic acid, ethyl ester (2.8 mmoles) in dimethyl formamide (10 ml) at ambient temperature was added 60% sodium hydride (0.12 g, 3.1 mmoles). After the gas evolution ceased, methyl iodide (0.44 g, 3.1 mmoles) was added and the reaction stirred at room temperature until complete by tlc (hexane/ethyl acetate). The reaction mixture was concentrated to dryness. The residue was partitioned between saturated sodium bicarbonate solution (10 ml) and methylene chloride (10 ml). The aqueous layer was again extracted with methylene chloride (3 x 10 ml). The organic layers were combined, dried using sodium sulfate, and concentrated to dryness. The residue that remained was purified by flash chromatography (hexane/ethyl acetate). Both isomers were isolated.

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

This compound was obtained from **17a** as a waxy, white solid in 19% yield, mp 79-81°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.25 (3H, CH_3, t), 2.33 (3H, CH_3, s), 3.93 (3H, CH_3, s), 4.23 (2H, CH_2, q).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.99; H, 5.73; N, 21.51.

3-Cyano-1,5-dimethyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14d**).

This compound was obtained from **17a** as gray needles in 63% yield after recrystallization from ethanol, mp 134-136°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.25 (3H, CH_3, t), 2.48 (3H, CH_3, s), 3.82 (3H, CH_3, s), 4.23 (2H, CH_2, q).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.73; H, 5.84; N, 21.54.

5-Cyano-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3f**).

This compound was obtained from **17c** as a white solid in 24% yield, mp 51-52°; ^{1}H nmr (deuteriochloroform): δ 1.33 (3H, CH_3, t), 4.08 (3H, CH_3, s), 4.32 (2H, CH_2, q), 7.41 (3H, ArH, m), 7.69 (2H, ArH, m).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.60; H, 5.21; N, 16.35.

3-Cyano-1-methyl-5-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14f**).

This compound was obtained from **17c** as white crystals in 53% yield, mp 101-103°; ^{1}H nmr (deuteriochloroform): δ 1.23 (3H, CH_3, t), 3.78 (3H, CH_3, s), 4.22 (2H, CH_2, q), 7.36 (2H, ArH, m), 7.51 (3H, ArH, m); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.02 (3H, CH_3, t), 3.72 (3H, CH_3, s), 4.06 (2H, CH_2, q), 7.49 (5H, ArH, m).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.80; H, 4.90; N, 16.69.

Preparation of 5-Chloro-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxaldehyde (**27b**).

Phosphorus oxychloride (16.86 g, 110 mmoles) was added dropwise to dimethyl formamide (8.04 g, 110 mmoles) maintaining a reaction temperature of less than 10°. The solution was stirred until it solidified. Compound **26b** [39] (55 mmoles) was added and the mixture heated at 70° for 17 hours. To this reaction mixture was added additional phosphorus oxychloride (33.73 g, 220 mmoles). The reaction mixture was heated at 100° for an additional 7 hours. The reaction was quenched into water (300 ml). The *p*H of the aqueous solution was adjusted to 7.0 using 50% sodium hydroxide. The neutralized solution was extracted with methylene chloride (5 x 100 ml), dried using sodium sulfate, and concentrated to dryness. The residue was dissolved in ethyl acetate and filtered through silica gel to remove impurities. The filtrate was concentrated to dryness and gave a solid product in 94% yield. A sample of this solid after recrystallization from hexane gave **27b**, mp 60-62°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.91 (3H, CH_3, s), 7.48 (3H, ArH, m), 7.76 (2H, ArH, m), 9.85 (1H, CHO, s).

Anal. Calcd. for $C_{11}H_9N_2OCl$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.73; H, 4.12; N, 12.70.

Preparation of 5-Chloro-1-methyl-3-phenyl-1H-pyrazole-4-carboxylic Acid (**28b**).

5-Chloro-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxylic acid **28b** was prepared similarly to the procedure of Huppatz [1] in 67% yield after recrystallization from water/acetic acid from 5-chloro-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxaldehyde **27b**, mp 172-175°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.88 (3H, CH_3, s), 7.40 (3H, ArH, m), 7.60 (2H, ArH, m), 12.74 (1H, CO_2H, s).

Anal. Calcd. for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.87; H, 3.96; N, 11.81.

Preparation of 5-Chloro-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**29b**).

5-Chloro-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxylic acid, ethyl ester **29b** was prepared similarly to the procedure of Huppatz [1] in 59% yield after flash chromatography using hexane/ethyl acetate (4:1) from 5-chloro-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxylic acid **28b**, mp 68-70°; ^{1}H nmr (deuteriochloroform): δ 1.22 (3H, CH_3, t), 3.91 (3H, CH_3, s), 4.24 (2H, CH_2, q), 7.39 (3H, ArH, m), 7.60 (2H, ArH, m).

Anal. Calcd. for $C_{13}H_{13}N_2O_2Cl$: C, 58.99; H, 4.95; N, 10.58. Found: C, 59.03; H, 5.01; N, 10.76.

General Procedure for the Preparation of 5-Cyano-1,3-dimethyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3d**) and 5-Cyano-1-methyl-3-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3f**) from **29a** and **29b**, respectively.

A suspension of **29a** or **29b** (5 mmoles), finely ground sodium cyanide (0.98 g, 20 mmoles), and 5 ml of dimethyl formamide was heated overnight at 150°. The reaction was quenched into water (100 ml). The aqueous solution was extracted with ether (4 x 25 ml). The combined organic layer was washed with water (5 x 25 ml) and concentrated to dryness.

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

This compound was prepared from **29a** and recrystallized from hexane to give **3d** in 34% yield, mp 81-82°; ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, CH_3, t), 2.49 (3H, CH_3, s), 4.02 (3H, CH_3, s), 4.36 (2H, CH_2, q); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.31 (3H, CH_3, t), 2.38 (3H, CH_3, s), 3.98 (3H, CH_3, s), 4.29 (2H, CH_2, q).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found C, 56.17; H, 5.92; N, 22.06.

5-Cyano-1-methyl-3-phenyl-1H-pyrazole-4-carboxylic Acid, Ethyl Ester (**3f**).

This compound was prepared from **29b** and purified using flash chromatography (hexane/ethyl acetate) to give **3f** in 41% yield, mp 50-52°; ^{1}H nmr (deuteriochloroform): δ 1.34 (3H, CH_3, t), 4.10 (3H, CH_3, s), 4.33 (2H, CH_2, q), 7.42 (3H, ArH, m), 7.71 (2H, ArH, m).

General Procedure for the Preparation of 5-[(Hydroximino)-(methylthio)methyl]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**12e**), 3-[(Hydroximino)(methylthio)-methyl]-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**15a**), and 1,3-Diphenyl-5- [(hydroximino)(methylthio)methyl]-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**12g**).

To a solution of 3 or 5-(*N*-Hydroxyaminothiocarbonyl)-1*H*-pyrazole-4 carboxylic Acid, Ethyl Ester **7e**, **7g**, and **13a** (1.45 mmoles) in methanol (20 ml) was added sodium methoxide (0.09 g, 1.6 mmoles) and iodomethane (0.25 g, 1.74 mmoles) and the reaction mixture was stirred at ambient temperature for 24 hours. The reaction was concentrated to dryness. The residue was dissolved in water (50 ml), the *p*H adjusted to 7.0, and extracted with methylene chloride (3 x 25 ml). Concentration of the organic layer gave the crude product which was purified by flash chromatography (hexane/ethyl acetate) or by recrystallization (hexane/ethyl acetate).

5-[(Hydroximino)(methylthio)methyl]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**12e**).

This compound was obtained from **7e** as a white powder in 37% yield after flash chromatography using hexane/ethyl acetate (4:1), mp 161-162°; ^{1}H nmr (deuteriochloroform): δ 1.30 (3H, CH_3, t), 1.86 (3H, CH_3, s), 2.55 (3H, CH_3, s), 4.26 (2H, CH_2, q), 7.40 (3H, ArH, m), 7.53 (2H, ArH, m), 9.53 (1H, NOH, s).

Anal. Calcd. for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16; S, 10.04. Found: C, 56.27; H, 5.55; N, 13.32; S, 10.07.

3-[(Hydroximino)(methylthio)methyl]-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**15a**).

This compound was obtained from **13a** as an oil in 59% yield after flash chromatography using ethyl acetate; ^{1}H nmr (deuteriochloroform): δ 1.21 (3H, CH_3, t), 1.91 (3H, CH_3, s), 3.85 (3H, CH_3, s), 4.17 (2H, CH_2, q), 7.91 (1H, CH, s), 9.85 (1H, NOH, s).

1,3-Diphenyl-5-[(hydroximino)(methylthio)methyl]-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**12g**).

This compound was obtained from **7g** as a white powder in 62% yield after recrystallization from hexane/ethyl acetate, mp 166-168°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.20 (3H, CH_3, t), 1.99 (3H, CH_3, s), 4.20 (2H, CH_2, q), 7.60 (10H, ArH, m), 12.16 (1H, NOH, s).

Anal. Calcd. for $C_{20}H_{19}N_3O_3S$: C, 62.97; H, 5.02; N, 11.02; S, 8.41. Found: C, 63.04; H, 5.04; N, 10.97; S, 8.37.

Preparation of 5-Formyl-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**10**).

A slurry of 5-hydroxymethyl-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid, ethyl ester **9** [10] (10.14 g, 39 mmoles),

pyridinium dichromate (73.36 g, 195 mmoles), and methylene chloride (250 ml) was stirred at room temperature for 6 days. The reaction was filtered through diatomaceous earth. The filtrate was concentrated to dryness. The residue was purified by flash chromatography (hexane/ethyl acetate). Further purification by recrystallization from hexane gave **10** as yellow powder, 3.58 g (36%), mp 74-77°; ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, CH_3, t), 2.55 (3H, CH_3, s), 4.41 (2H, CH_2, q), 7.40 (5H, ArH, m), 10.44 (1H, CHO, s).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.09; H, 5.48; N, 10.79.

Preparation of 5-[(Hydroxyimino)methyl]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**11**).

Hydroxylamine hydrochloride (1.04 g, 15 mmoles), pyridine (1.19 g, 15 mmoles) and ethanol (10 ml) were combined and stirred for 30 minutes at ambient temperature. To this solution was added 5-formyl-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid, ethyl ester **10** (1.94 g, 7.5 mmoles) in ethanol (5 ml). The reaction was stirred for 16 hours at ambient temperature. The reaction was concentrated to dryness. The residue was suspended in water (30 ml) and filtered. The cake was washed with water (30 ml), propanol (30 ml), and dried in vacuum at 40° and gave **11** as a tan powder, 1.78 g (87%), mp 247-248; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.26 (3H, CH_3, t), 2.37 (3H, CH_3, s), 4.22 (2H, CH_2, q), 7.42 (5H, ArH, m), 8.37 (1H, CH=N, s), 11.68 (1H, NOH, s).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.37. Found: C, 61.74; H, 5.61; N, 15.11.

Preparation of 3-[(Hydroxyimino)methyl]-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**31**).

A slurry of hydroxylamine hydrochloride (12.93 g, 18.6 mmoles), 3-formyl-1-methyl-1*H*-pyrazole-4-carboxylic acid, ethyl ester **30** [40] (16.97 g, 93 mmoles) and ethanol (93 ml) was stirred 24 hours at ambient temperature. The reaction was concentrated to dryness. The residue was dissolved in 1*N* sodium hydroxide solution (150 ml) and extracted with ethyl acetate (3 x 100 ml). The organic extract was dried using sodium sulfate and concentrated to dryness. Purification by recrystallization from ethyl acetate gave 10.23 g of **31** in 56% yield, mp 153-155°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.22 (3H, CH_3, t), 3.83 (3H, CH_3, s), 4.17 (2H, CH_2, q), 8.28 (1H, CH, s), 8.36 (1H, CH=N, s), 11.35 (1H, NOH, s).

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.56; H, 5.59; N, 21.08.

General Procedure for the Preparation of 5-Cyano-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**3e**) and 3-Cyano-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14a**) from **11** and **31**, respectively.

Acetic anhydride (12 ml) and the oxime (1 mmole) were combined and heated at reflux for 5 hours. The solution was concentrated to dryness. The residue was purified by flash chromatography (hexane/ethyl acetate). Further purification was achieved by recrystallization from hexane.

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

This compound was obtained from **11** as a white powder in 77% yield, mp 86-87°; ^{1}H nmr (deuteriochloroform): δ 1.37 (3H, CH_3, t), 2.54 (3H, CH_3, s), 4.36 (2H, CH_2, q), 7.48 (3H, ArH, m), 7.66 (2H, ArH, t).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.71; H. 5.15; N, 16.50.

3-Cyano-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**14a**).

This compound was obtained from **31** as tan plates in 89% yield, mp 90-92°; ^{1}H nmr (deuteriochloroform): δ 1.38 (3H, CH_3, t), 3.99 (3H, CH_3, s). 4.35 (2H, CH_2, q), 7.93 (1H, CH, s).

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.53; H, 5.23; N, 23.17. Found: C, 53.63; H, 5.06; N, 23.45.

Preparation of 1,3-Diphenyl-5-(methylbromo)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**33a**).

A suspension of 1,3-diphenyl-5-methyl-1*H*-pyrazole-4-carboxylic acid, ethyl ester **32a** [32] (6.88 g, 22.5 mmoles), 1,3-dibromo-5,5-dimethyl hydantoin (3.21 g, 11.2 mmoles), benzoyl peroxide (0.04 g) and carbon tetrachloride (120 ml) was stirred at reflux for 16 hours. The reaction mixture was cooled, washed with water (2 x 50 ml), and concentrated to dryness. Recrystallization from methanol gave a tan powder, 7.48 g (86%), mp 103-105°; ^{1}H nmr (deuteriochloroform): δ 1.28 (3H, CH_3, t), 4.30 (2H, CH_2, q), 4.76 (2H, CH_2, s), 7.50 (10H, ArH, m).

Anal. Calcd. for $C_{19}H_{17}N_2O_2Br$: C, 59.23; H, 4.45; N, 7.27; Br, 20.74. Found: C, 59.48; H, 4.48; N, 7.23; Br, 20.94.

Preparation of 1,3-Diphenyl-5[(hydroximino)methyl]-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**34a**).

1,3-Diphenyl-5[(hydroxamino)methyl]-1*H*-pyrazole-4-carboxylic acid, ethyl ester (**34a**) was prepared similarly to the procedure of Beck [43]. Thus, to a solution of sodium methoxide (1.37 g, 25.3 mmoles) and ethanol (42 ml) was added dropwise 2-nitropropane (2.25 g, 18.1 mmoles). The thick suspension was stirred for 1 hour at ambient temperature. The 1,3-diphenyl-5-(methylbromo)-1*H*-pyrazole-4-carboxylic acid ethyl ester 33a (6.98 g, 18.1 mmoles) was added and the reaction heated at reflux for 16 hours. The reaction mixture was concentrated to dryness and partitioned between water (100 ml) and diethyl ether (3 x 100 ml). The organic layers were washed with water (2 x 50 ml), dried using sodium sulfate, and concentrated to an oil. The oil was dissolved in ethanol (36 ml). Hydroxylamine hydrochloride (2.52 g, 36.2 mmoles) was added and the reaction was stirred for 2 days at ambient temperature. The reaction mixture was concentrated to dryness. The residue was dissolved in 1*N* sodium hydroxide (50 ml) and extracted with ethyl acetate (3 x 25 ml). The organic layer was concentrated to dryness, and the residue was purified by flash chromatography (toluene/ethyl acetate) and recrystallized (hexane/ethyl acetate) to give **34a** as white needles 3.06 g in 50% yield, mp 140-142°; ^{1}H nmr (deuteriochloroform): δ 1.21 (3H, CH_3, t), 4.26 (2H, CH_2, q), 7.43 (8H, ArH, m), 7.68 (2H, ArH, m), 8.43 (1H, CH, s), 8.51 (1H, NOH, s).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.04; H, 5.11; N, 12.53. Found: C, 68.32; H, 5.31; H, 12.50.

General Procedure for the Preparation of 1-(1,1-Dimethylethyl)-5-(*N*-hydroxyaminothiocarbonyl)1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7c**), 5-(*N*-Hydroxyaminothiocarbonyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7e**), 1,3-Diphenyl-5-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7g**), and 3-(*N*-Hydroxyaminothiocarbonyl)-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**13a**) from **34b**, **11**, **34a**, and **31**, respectively.

A solution of the oxime **11**, **31**, **34a**, or **34b** (3.5 mmoles), dimethyl formamide (20 ml), and *N*-chlorosuccinimide (0.47 g, 3.5 mmoles) was stirred for 2 hours at ambient temperature. The reaction was diluted with water (80 ml) and extracted with diethyl ether (4 x 20 ml). The organic layers were combined, washed with water (4 x 20 ml), dried with sodium sulfate and concentrated to dryness. The residue was dissolved in ethanol (2 ml) and added to a solution of sodium hydrosulfide (0.86 g, 15.4 mmoles) in water (20 ml). The reaction mixture was diluted with water (80 ml). The *p*H of the solution was adjusted to 10.5 using 5*N* sodium hydroxide solution and extracted with diethyl ether (3 x 50 ml). The *p*H of the aqueous layer was adjusted to 5.0 using acetic acid and the product extracted with diethyl ether (3 x 50 ml). The organic layers were combined, dried using sodium sulfate, and concentrated to dryness. The residue was recrystallized (hexane/ethyl acetate).

1-(1,1-Dimethylethyl)-5-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4 carboxylic Acid, Ethyl Ester (**7c**).

This compound was obtained from **34b** [43] as a white granular solid in 27% yield, mp 113-115°; ^{1}H nmr (deuteriochloroform): δ 1.25 (3H, CH_3, t), 1.62 (9H, CH_3, s), 4.1 (2H, CH_2, q), 7.8 (1H, CH, s).

Anal. Calcd. for $C_{11}H_{17}N_3O_3S$: C, 48.69; H, 6.31; N, 15.49; S, 11.82. Found: C, 48.56; H, 6.39; N, 15.37; S, 12.10.

5-(*N*-Hydroxyaminothiocarbonyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7e**).

This compound was obtained from **11** as a tan powder in 30% yield mp 158-160°; ^{1}H nmr (deuteriochloroform): δ 1.38 (3H, CH_3, t), 2.51 (3H, CH_3, s), 4.35 (2H, CH_2, q), 7.41 (5H, ArH, s).

Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; S, 10.50. Found: C, 54.95; H, 4.83; N, 13.87; S, 10.22.

1,3-Diphenyl-5-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**7g**).

This compound was obtained from **34a** as yellow needles in 53% yield, mp 157-159°; ^{1}H nmr (deuteriochloroform): δ 1.15 (3H, CH_3, t), 4.22 (2H, CH_2, q), 7.5 (10H, ArH, m).

Anal. Calcd. for $C_{19}H_{17}N_3O_3S$: C, 62.11; H, 4.66; N, 11.43; S, 8.73. Found: C, 62.08; H, 4.79; N, 11.29; S, 8.71.

3-(*N*-Hydroxyaminothiocarbonyl)-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**13a**).

This compound was obtained from **31** as a yellow solid in 17% yield, mp 134-136°; ^{1}H nmr (deuteriochloroform): δ 1.38 (3H, CH_3, t), 4.03 (3H, CH_3, s), 4.35 (2H, CH_3, q), 8.02 (1H, CH, s).

Anal. Calcd. exact mass for $C_8H_{12}N_3O_3S$ = 230.0599. Exact mass found by mass spectrometry: $C_8H_{12}N_3O_3S$ = 230.0587.

General Procedure for the Preparation of 5-[(Hydroximino)-(methylthio)methyl]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**12e**), 3-[(Hydroximino)(methylthio)-methyl]-1-methyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**15a**), and 1,3-Diphenyl-5-[(hydroximino)(methylthio)methyl]-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**12g**) from **11**, **31**, and **34a**, respectively.

A solution of oxime **11**, **31**, or **34a** (2.5 mmoles), *N*-chlorosuccinimide (0.33 g, 2.5 mmoles) and dimethyl formamide (20 ml) was stirred at ambient temperature for 1.5 hours. The reaction was diluted with water (80 ml) and extracted with diethyl ether (4 x 20 ml). The organic layers were combined, washed with water (2 x 20 ml), dried using sodium sulfate, and concentrated to dryness. The residue was dissolved in methanol (2 ml) and reacted similarly to the procedure of Davies [19] with a saturated solution of methanethiol in methanol (20 ml) containing sodium methoxide (0.19 g, 3.5 mmoles). The reaction mixture was stirred at ambient temperature for 1 hour. The reaction was concentrated to dryness. The residue was dissolved in water (50 ml) and the *p*H was adjusted to 7.0 using 0.1*N* sodium hydroxide. The resulting solution was extracted with methylene chloride (3 x 30 ml). The combined organic layers were concentrated to an oil. The oil was purified by flash chromatography (hexane/ethyl acetate).

5-[(Hydroximino)(methylthio)methyl]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**12e**).

This compound was obtained from **11** as colorless crystals in 43% yield after flash chromatography using hexane/ethyl acetate (3:1) and recrystallization from hexane/ethyl acetate (1:1), mp 161-163°; ^{1}H nmr (deuteriochloroform): δ 1.30 (3H, CH_3, t), 1.88 (3H, CH_3, s), 2.54 (3H, CH_3, s), 4.28 (2H, CH_2, q), 7.42 (3H, ArH, m), 7.54 (2H, ArH, m), 9.54 (1H, NOH, s).

Anal. Calcd. for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.36; N, 13.16; S, 10.04. Found: C, 56.69; H, 5.42; N, 13.14; S, 10.11.

3-[(Hydroximino)(methylthio)methyl]-1-methyl-1*H*-pyrazole-4 carboxylic Acid, Ethyl Ester (**15a**).

This compound was obtained from **31** as an oil in 43% yield after flash chromatography using toluene/tetrahydrofuran (3:2); ^{1}H nmr (deuteriochloroform): δ 1.26 (3H, CH_3, t), 1.97 (3H, CH_3, s), 3.91 (3H, CH_3, s), 4.22 (2H, CH_2, q), 7.93 (1H, CH, s), 9.66 (1H, NOH, s).

Anal. Calcd. exact mass for $C_9H_{14}N_3O_3S$ = 244.0756. Exact mass found by mass spectrometry: $C_9H_{14}N_3O_3S$ = 244.0753.

1,3-Diphenyl-5-[(hydroximino)(methylthio)methyl]-1*H*-pyrazole-4 carboxylic Acid, Ethyl Ester (**12g**).

This compound was obtained from **34a** in 26% yield after flash chromatography using hexane/ethyl acetate, mp 166-169°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.19 (3H, CH_3, t), 2.00 (3H, CH_3, s), 4.20 (2H, CH_2, q), 7.60 (10H, ArH, m), 12.17 (1H, OH, s).

Anal. Calcd. for $C_{20}H_{19}N_3O_3S$: C, 62.97; H, 5.02; N, 11.02; S, 8.41. Found: C, 63.21; H, 5.08; N, 11.20; S, 8.39.

Acknowledgements.

We thank Mr. Thomas M. Wilson for assistance with the long range HETCOR experiments. We also thank Professors Leo Paquette and Edward C. Taylor for their helpful discussions.

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