Chemistry of Amino Acid Thionoester Derivatives. An Unexpected Change in the Reaction Course Between Heterocyclic-2-carboxylic Acid Hydrazides and *N*-Substituted Thionoglycinates. Preferential Formation of 4-Amino-1,2,4-triazole Adducts over 1,3,4-Oxadiazole Products

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The reaction between benzoic acid hydrazides and ethyl *N*-carbobenzyloxythionoglycinate produces the expected 2-aminomethyl-1,3,4-oxadiazoles in good yield. Heterocyclic carboxylic acid hydrazides give similar products when the hydrazide moiety is located at either the three or four position (relative to the heteroatom) in the ring. However, when heterocyclic-2-carboxylic acid hydrazides are utilized, oxadiazole formation is dramatically reduced. Instead, the intermediate imidates are usually isolated as the major products of the reaction from one equivalent of these hydrazides. These imidate products are accompanied by significant amounts of 4-amino-1,2,4-triazole derivatives which arise from incorporation of two equivalents of the hydrazide. The structure of these unexpected 4-aminotriazole products was confirmed by nmr and mass spectral data as well as an X-ray analysis. In the presence of a stoichiometric amount of these hydrazides, the 4-aminotriazoles become the major products of the reaction. This phenomenon was found to be general for 2-thienyl, 2-furoic, picolinic, and pyrazinoic acid hydrazides. The intermediate imidates for each of these systems were isolated, characterized and found to have a remarkable thermal stability. Conversion of these imidates to the corresponding 1,3,4-oxadiazoles could only be accomplished in hot acetic anhydride. A mechanistic rationale is presented which suggests that some stabilization of the intermediate imidate must occur in these examples which allows an intermolecular process to compete so effectively with an intramolecular cyclization. Since the cyclization to oxadiazole is presumed to be acid catalyzed, this stabilization is proposed to occur specifically by the formation of a hydrogen bond between the ring heteroatom and the protonated imino nitrogen present in the imidate prior to cyclization. The formation of such a hydrogen bond removes the carboxylate oxygen from its opportune position for cyclization, while the protonated imino nitrogen can still activate the imidate for subsequent reaction with a second equivalent of hydrazide. In all cases where this heteroatom is capable of hydrogen bond formation, 4-aminotriazoles predominate. The relative amount of 4-aminotriazole product is directly correlatable with the donor capability of the ring heteroatom. This proposed model was tested by examining a system where steric congestion would be expected to prevent hydrogen bond formation. Indeed, when *N*-methyl-2-pyrrole carboxylic acid hydrazide was utilized in the reaction, the corresponding 1,3,4-oxadiazole was formed as expected in high yield. Conversely, an acyclic aliphatic hydrazide specifically bearing a *beta* heteroatom (*N*-carbobenzyloxyglycine hydrazide) produced the expected 4-aminotriazole adduct in high yield. This therefore appears to be a general phenomenon which provides a useful synthetic entry to several new unsymmetrically substituted 4-amino-1,2,4-triazole derivatives.

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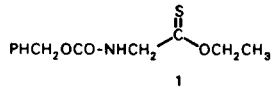
While many *N*-protected amino acid thionoesters have been reported in the literature [1,2], their synthetic utility has been largely limited to the preparation of various thioamide and thiopeptide derivatives. Thionoesters have been used successfully in other systems as versatile intermediates to prepare a wide variety of heterocycles [3,4,5]. Consequently, we felt that *N*-substituted aminoacid thionoesters could provide a direct access to certain heterocycles containing aminoalkyl sidechains. To test this approach, we undertook a systematic study of the heterocycle-forming reactions of the known [1a] thionoester, ethyl *N*-carbobenzyloxythionoglycinate (**1**).



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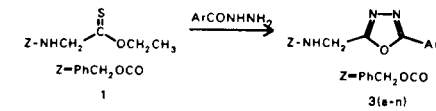
Indeed, we found this intermediate to be quite useful for the preparation of many interesting aminomethylheterocycles [6]. For example, reaction with a series of benzoic acid hydrazides **2** produced the expected 1,3,4-oxadiazoles **3** in good yield (Table 2) as shown below. While the reaction can be run in either protic or aprotic solvents, consistently good yields were obtained using refluxing acetonitrile.



1 3(a-n)

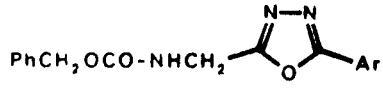
The gaseous hydrogen sulfide produced seems to facilitate the reaction and can be easily trapped and neutralized through a bubbler. Any unreacted thionoester can

Table 1

Product Distribution from the Reaction of Heterocyclic 2-Carboxylic Acid Hydrazides with Ethyl *N*-Carbobenzyloxythionoglycinate

Thionoester (mmoles)	Hydrazide (mmoles)	Oxadiazole No. (mmoles)	Imidate No. (mmoles)	*N*-Aminotriazole No. (mmoles)	Thionoester Recovered (mmoles)
	2-thienyl	**3p**	**5a**	**4a**	
(10)	(10)	(3.8)	(1.9)	(1.6)	(2.0)
(10)	(20)	(3.2)	(1.9)	(4.6)	(0.1)
	2-furyl	**3q**	**5b**	**4b**	
(10)	(10)	(1.0)	(3.2)	(2.3)	(3.3)
(10)	(20)	(0.7)	(2.3)	(6.4)	(0.1)
	2-pyridyl	**3r**	**5c**	**4c**	
(10)	(10)	(0.8)	(3.8)	(2.1)	(2.2)
(10)	(20)	(0.5)	(2.8)	(5.2)	(0.4)
	2-pyrazinyl	**3s**	**5d**	**4d**	
(10)	(10)	(1.3)	(2.4)	(3.0)	(2.8)
(10)	(20)	(1.1)	(1.1)	(7.5)	(0.2)

Table 2



Ar	No.	Mp °C	Yield (%)	^{1}H NMR δ, ppm d_6 DMSO		Mass Spectra m/e	Empirical Formula	Analyses (%) Calcd./Found C	H	N
phenyl [8]	**3a**	123-124	80	7.89 (m, 6H) 7.35 (s, 5H)	5.10 (s, 2H) 4.58 (d, 2H)	309	$C_{17}H_{15}N_3O_3$	66.01 	4.89 	13.58
p-methylphenyl	**3b**	130-132	68	7.83 (m, 10H) 4.60 (d, 2H)	5.13 (s, 2H) 2.40 (s, 3H)	323	$C_{18}H_{17}N_3O_3$	66.86 66.78	5.30 5.32	13.00 12.97
m-nitrophenyl	**3c**	152-153	66	8.90 (m, 5H) 7.35 (s, 5H)	5.10 (s, 2H) 4.62 (d, 2H)	354	$C_{17}H_{14}N_4O_5$	57.63 57.62	3.98 3.99	15.81 15.80
p-methoxyphenyl	**3d**	121-121.5	64	7.53 (q, 5H) 7.37 (s, 5H) 3.83 (s, 3H)	5.12 (s, 2H) 4.57 (d, 2H)	339	$C_{18}H_{17}N_3O_4$	63.71 63.66	5.05 5.08	12.38 12.36
p-aminophenyl	**3e**	158-161	75	8.07 (t, 1H) 7.22 (q, 4H) 5.13 (s, 2H)	7.40 (s, 5H) 5.92 (s, 2H) 4.55 (d, 2H)	324	$C_{17}H_{16}N_4O_3$	62.96 62.78	4.97 5.01	17.27 17.24
1,1'-biphenyl-4-yl	**3f**	119-121	70	7.75 (m, 15H) 4.58 (d, 2H)	5.08 (s, 2H)	385	$C_{23}H_{19}N_3O_3$	71.68 71.66	4.97 4.98	10.90 10.93
1,3-benzodioxol-5-yl	**3g**	121-123	73	8.00 (t, 1H) 6.13 (s, 2H) 4.53 (d, 2H)	7.38 (m, 8H) 5.10 (s, 2H)	353	$C_{18}H_{15}N_3O_5$	61.19 61.05	4.28 4.35	11.89 11.87
o-methylphenyl	**3h**	123-125	43 [a]	8.07 (t, 1H) 5.00 (s, 2H) 2.33 (s, 3H)	7.56 (m, 9H) 4.48 (d, 2H)	323	$C_{18}H_{17}N_3O_3$	66.86 66.78	5.30 5.34	13.00 12.96
o-chlorophenyl	**3i**	51-53	53 [a]	7.92 (m, 5H) 7.33 (s, 5H)	5.10 (s, 2H) 4.62 (d, 2H)	343	$C_{17}H_{14}ClN_3O_3$	59.40 59.39	4.11 4.15	12.22 12.19
o-phenoxyphenyl	**3j**	93-95	46 [a]	7.33 (m, 15H) 4.50 (d, 2H)	5.03 (s, 2H)	401	$C_{23}H_{19}N_3O_4$	68.82 68.88	4.77 5.02	10.47 10.67
2,5-dichlorophenyl	**3k**	109-110	45 [a]	8.12 (t, 1H) 7.32 (s, 5H) 4.58 (d, 2H)	7.95 (m, 3H) 5.00 (s, 2H)	377	$C_{17}H_{13}Cl_2N_3O_3$	53.99 53.93	3.46 3.54	11.11 11.07

Table 2 (continued)

Ar	No.	Mp °C	Yield (%)	^{1}H NMR δ, ppm d_6 DMSO		Mass Spectra m/e	Empirical Formula	Analyses (%) Calcd./Found C	H	N
3-pyridyl [8]	**3l**	135-136	54	7.92 (m, 4H) 5.07 (s, 2H)	7.37 (s, 5H) 4.58 (d, 2H)	310	$C_{16}H_{14}N_4O_3$	61.93	4.55	18.06
4-pyridyl [8]	**3m**	117-118	45	8.82 (m, 2H) 7.35 (s, 5H) 4.62 (d, 2H)	7.88 (m, 3H) 5.07 (s, 2H)	310	$C_{16}H_{14}N_4O_3$	61.93	4.55	18.06
3-furyl	**3n**	93-94	42	8.02 (t, 1H) 5.10 (s, 2H)	7.45 (m, 8H) 4.58 (d, 2H)	299	$C_{15}H_{13}N_3O_4$	60.20 60.23	4.38 4.42	14.04 14.02
N-methyl-pyrrol-2-yl	**3o**	94-96	68	8.08 (t, 1H) 7.13 (s, 1H) 6.20 (t, 1H) 4.49 (d, 2H)	7.36 (s, 5H) 6.72 (d, 1H) 5.08 (s, 2H) 3.93 (s, 3H)	312	$C_{16}H_{16}N_4O_3$	61.53 61.52	5.16 5.18	17.94 17.91

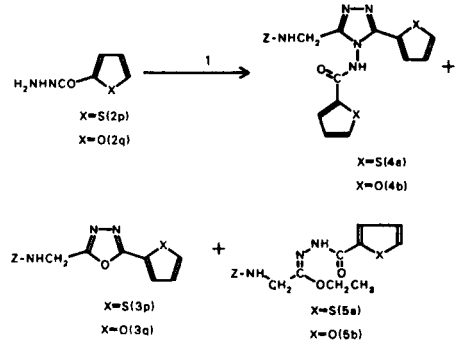
[a] Solvent = Dimethylformamide.

also be conveniently removed by simply washing the crude reaction product with diethyl ether. When the reaction is complete, the solution is concentrated. Trituration of the crude product with ethereal ethanol generally causes the material to crystallize. One recrystallization from ethanol produces analytically pure product. A chromatographic purification was required in only one instance (**3e**). This thionoester, therefore, offers significant advantages over its imidate precursor [7] for the ease in isolation of the products. Consequently, the overall percent yields of oxadiazole obtained *via* this thionoester are higher than those reported for the corresponding imidate [8]. Many of these reactions have been successfully run on scales up to 1 mole.

The reaction tolerates a wide variety of functional groups. Even strongly electron-withdrawing or electron-donating substituents can be accomodated. Bulky *ortho* substituents may also be present. However, in such cases, it is necessary to utilize a higher-boiling solvent such as dimethylformamide to maximize the conversion to product. Certain heterocyclic carboxylic acid hydrazides also produce the expected oxadiazole products **3l-n** in comparable yield. In all cases, formation of the cyclized product is easily confirmed because of the distinct downfield shift observed for the glycine methylene protons by nmr.

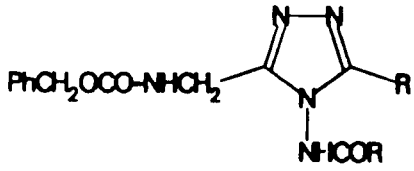
However, when thionoester **1** was treated with one equivalent of thiophene-2-carboxylic acid hydrazide **2p**, another product was produced unexpectedly in significant amounts (Scheme 1). The nmr and mass spectral characterization of this material indicated that a second equivalent of the hydrazide had been incorporated into the product. An X-ray analysis (Figure 1) of this substance confirmed the proposed structure as a 4-amino-1,2,4-triazole (**4a**). Careful examination of the crude reaction mixture by preparative tlc demonstrated that some oxadiazole product **3p** was present but in substantially lower yield (Table 1). Significant amounts of the intermediate imidate **5a** were also present in the mixture. The stoichiometry leading to this triazole product dictates that some thionoester remain unreacted. This was also observed. As expected, the yield of 4-aminotriazole can be increased significantly by utilizing a stoichiometric amount (two equivalents) of hydrazide in the reaction. Under these conditions, essentially all of the thionoester is consumed, and the 4-aminotriazole clearly becomes the major product of the reaction.

SCHEME 1



In the case of 2-furoic acid hydrazide **2q**, formation of the oxadiazole product **3q** is even less favored. Reaction between thionoester **1** and one equivalent of this hydrazide (Scheme 1) produces the imidate **5b** as the major product (Table 1) along with a significant amount of the 4-aminotriazole **4b**. Once again, a corresponding amount of unreacted thionoester was recovered. The expected oxadiazole was present in only small quantity (10%) but could be easily isolated by preparative tlc. When two

Table 3



R	No.	Mp °C	Yield [a] (%)	^{1}H NMR δ, ppm d_6 DMSO		Mass Spectra m/e	Empirical Formula	Analyses (%) Calcd./Found C	H	N
2-thienyl	**4a**	215-217	46	12.76 (s, 1H) 7.96 (t, 1H) 7.64 (d, 1H) 7.20 (t, 1H) 4.38 (d, 2H)	8.04 (dd, 2H) 7.77 (d, 1H) 7.34 (m, 6H) 4.95 (s, 2H)	439	$C_{20}H_{17}N_5O_3S_2$	54.65 54.71	3.90 3.97	15.93 15.87
2-furyl	**4b**	152-154	64	12.50 (s, 1H) 7.90 (m, 1H) 7.33 (m, 6H) 6.76 (dd, 1H) 5.00 (s, 2H)	8.07 (s, 1H) 7.42 (d, 1H) 6.95 (dd, 1H) 6.65 (dd, 1H) 4.42 (d, 2H)	407	$C_{20}H_{17}N_5O_5$	58.97 58.97	4.21 4.15	17.19 17.19
2-pyridyl	**4c**	185-187	52 75 [b]	8.92 (d, 1H) 7.95 (mm, 6H) 5.08 (s, 2H)	8.52 (d, 1H) 7.45 (m, 6H) 4.53 (d, 2H)	429	$C_{22}H_{19}N_7O_3$	61.53 61.49	4.46 4.46	22.83 22.80
2-pyrazinyl	**4d**	113-115	75	8.97 (mm, 7H) 7.30 (s, 5H) 4.48 (d, 2H)	7.83 (t, 1H) 4.95 (s, 2H)	431	$C_{20}H_{17}N_9O_3$	55.68 55.63	3.97 4.02	29.22 29.19
PhCH$_2$OCONHCH$_2$-	**4e**	156-157	69	7.70 (t, 2H) 5.07 (s, 6H) 3.90 (d, 2H)	7.37 (s, 15H) 4.23 (d, 4H) 3.33 (s, 1H)	601	$C_{30}H_{31}N_7O_7$	59.89 59.67	5.19 5.35	16.30 16.35
H	**4f**	180-182	59	8.65 (s, 1H) 7.82 (t, 1H) 5.07 (s, 2H)	8.35 (s, 1H) 7.37 (s, 5H) 4.27 (d, 2H)	275	$C_{12}H_{13}N_5O_3$	52.36 52.53	4.76 4.81	25.44 25.40

[a] Solvent = Acetonitrile [b] Solvent = Pyridine

equivalents of hydrazide were employed, all of the thionoester was consumed, and the 4-aminotriazole again becomes the major isolated product. Both ^{1}H and ^{13}C nmr as well as mass spectral data were consistent with the formation of this 2:1 adduct. The ^{13}C nmr data for this product compared quite favorably for that observed earlier for the triazole product obtained from thiophene 2-carboxylic acid hydrazide (Table 4).

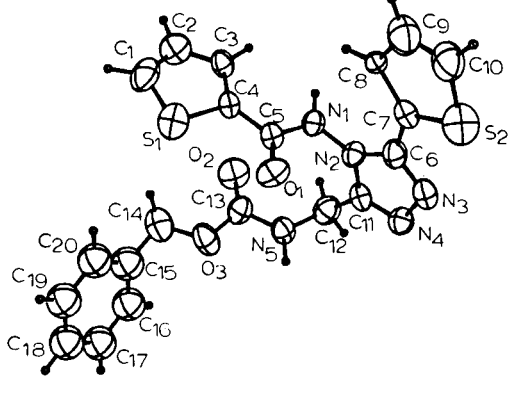
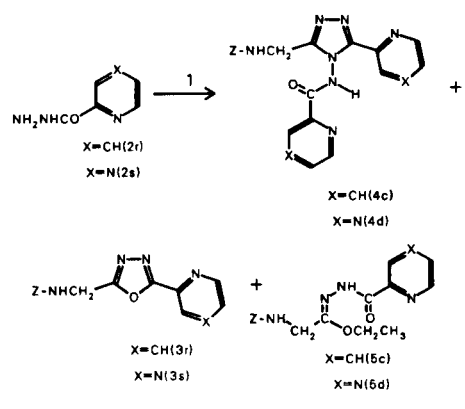


Figure 1. X-ray Crystal Structure of **4a**.

Similar results were observed with the corresponding six-membered ring heterocyclic acid hydrazides (Scheme 2). Once again, oxadiazole formation is clearly the less favored process. Treatment of thionoester **1** with one equivalent of picolinic acid hydrazide **2r** [9] produces the imidate **5c** as the major product (Table 1) along with a significant amount of the triazole adduct **4c**. Very little oxadiazole **3r** formation was observed. When two equiva-

SCHEME 2

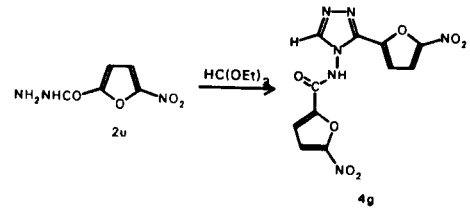


lents of this hydrazide were utilized, all of the thionoester was consumed, and higher amounts of the triazole product were obtained. The isolated yield of triazole could be increased significantly in this case by performing the reaction in refluxing pyridine.

When 2-pyrazinoic acid hydrazide (**2s**) [10] was utilized in the reaction, the imidate **5d** and triazole **4d** were again the major products isolated. When two equivalents of this hydrazide were employed, a highly selective transformation occurred which resulted in the formation of the 2:1 triazole adduct in very good yield. As before, both nmr and mass spectral data for these triazoles were fully consistent with pure products (Table 3,4).

With picolinic acid hydrazide *N*-oxide (**2t**) [11], the intermediate imidate **5e** was the only product isolated. The extremely low solubility of this material caused it to precipitate from the solution as it formed. This presumably prevented any subsequent transformation from occurring.

A search [12] of the literature revealed that this type of triazole product had only been observed one other time [13]. Treatment of 5-nitro-2-furoic acid hydrazide (**2u**) with excess ethylorthoformate in acidic ethanol at reflux produces the corresponding 4-aminotriazole **4g** in good yield as shown below.



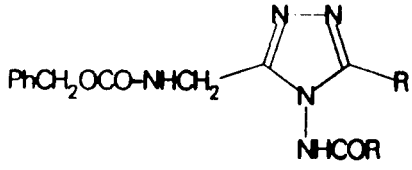
Once again, a heterocyclic 2-carboxylic acid hydrazide is implicated in 4-aminotriazole formation. This result also indicates that the formation of a 2:1 triazole adduct occurs independently of the aminoalkyl side chain present in thionoester **1**.

The formation of these reaction products was quite surprising. These experimental observations suggested quite strongly that a partitioning in reaction course was occurring when heterocyclic-2-carboxylic acid hydrazides were utilized. Indeed, in such cases, it seemed that a bimolecular intermolecular process to produce 4-aminotriazole was favored over an intramolecular cyclization to form oxadiazole. This is a relatively rare occurrence in organic chemistry which warranted further investigation.

In order to more fully understand the factors controlling this partitioning, the previously described reaction between thionoester **1** and nicotinic acid hydrazide (**2l**) was

Table 4

^{13}C NMR Chemical Shifts for:

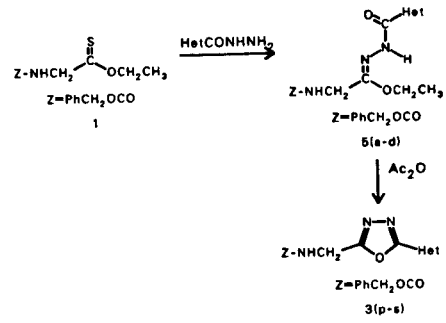


R	No.	^{13}C NMR δ, ppm d_6-DMSO-(TMS)							
2-thienyl	**4a**	160.25	156.12	153.01	149.01	136.76	134.81	133.49	131.09
		129.32	128.48	128.31	128.09	127.80	127.32	126.20	65.67
		34.65							
2-furyl	**4b**	156.38	156.03	152.78	146.96	146.08	145.12	144.71	140.14
		136.72	128.44	128.24	127.71	116.83	112.32	111.83	111.21
		65.61	34.49						
2-pyridyl	**4c**	163.62	156.12	153.92	150.99	149.22	148.84	148.03	146.14
		137.90	137.26	136.87	128.30	127.71	127.59	124.67	122.84
		122.66	65.59	34.76					
2-pyrazinyl	**4d**	162.58	156.07	154.48	149.10	148.60	145.48	144.19	144.02
		143.74	143.35	143.02	141.87	136.79	128.29	127.79	127.69
		65.56	34.56						
PhCH$_2$OCONHCH$_2$-	**4e**	168.69	156.64	156.06	152.11	136.78	136.66	128.24	127.74
		65.67	34.34						
H	**4f**	160.07	155.99	151.09	144.37	136.73	130.25	128.22	127.69
		65.61	34.05						

reinvestigated. Once again, only the oxadiazole product **3l** was isolated. No 4-aminotriazole product could be detected, even when two equivalents of this hydrazide were utilized. In this case, all of the excess hydrazide was recovered from the reaction. This oxadiazole **3l** was also treated with one equivalent of 2-furoic acid hydrazide (**2q**) in acetonitrile at reflux. Again, each reactant was recovered unchanged. There was no indication that a second hydrazide molecule could react with the product oxadiazole to form a 4-aminotriazole adduct under the typical reaction conditions. These results strongly implicate the intermediate imidate as the branchpoint for the change in reaction course.

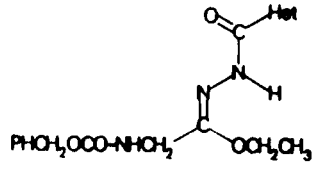
Consequently, each heterocyclic 2-carboxylic acid hydrazide was converted independently to the corresponding imidates **5a-d** by a low temperature reaction with one equivalent of thionoester **1** in ethanol (Table 5). These isolated imidates possessed a remarkable thermal stability for aliphatic imidates. For example, when heated either in solution or neat *in vacuo* (0.1 Torr) above their melting point, they could be recovered unchanged with little, if any, decomposition. Absolutely no conversion to oxadiazole products was observed under these conditions. However, a clean transformation to the corresponding oxadiazoles **3p-s** was observed (Scheme 3) when these imidates were heated for a few hours in acetic anhyride (Table 6). Thus, it was clear that these intermediates could form oxadiazole products under the proper conditions.

SCHEME 3



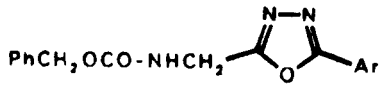
From these results we propose that the reaction between thionoester **1** and any aromatic carboxylic acid hydrazide proceeds to produce the intermediate imidates in solution. Presumably, subsequent cyclization to an oxadiazole product requires acid catalysis, specifically by protonation at the imino nitrogen. It is at this point that a partitioning in reaction course can occur. With most aromatic acid hydrazides, the reaction proceeds from this point to give the expected oxadiazole after cyclization. However, this protonated intermediate can be stabilized by hydrogen bond-

Table 5



Het	No.	Mp °C	Yield (%)	^{1}H NMR δ, ppm d_6 DMSO	Mass Spectra m/e	Empirical Formula	Analyses (%) Calcd./Found C	H	N
2-thienyl	**5a**	144	59	7.72 (m, 3H) 7.28 (s, 5H) 7.12 (q, 1H) 5.03 (s, 2H) 4.12 (q, 2H) 3.92 (d, 2H) 1.27 (t, 3H)	361	$C_{17}H_{19}N_3O_4S$	56.49 56.57	5.30 5.30	11.63 11.62
2-furyl	**5b**	136	38	7.95 (m, 2H) 7.28 (m, 6H) 6.45 (q, 1H) 5.07 (s, 2H) 4.18 (q, 2H) 4.02 (d, 2H) 1.22 (t, 3H)	345	$C_{17}H_{19}N_3O_5$	59.12 59.13	5.55 5.56	12.17 12.15
2-pyridyl	**5c**	120-121	68	10.83 (s, 1H) 8.05 (m, 5H) 7.32 (s, 5H) 5.08 (s, 2H) 4.28 (q, 2H) 4.12 (d, 2H) 1.32 (t, 3H)	356	$C_{18}H_{20}N_4O_4$	60.66 60.79	5.66 5.71	15.72 15.93
2-pyrazinyl	**5d**	151-153	65	9.27 (s, 1H) 8.95 (d, 1H) 8.83 (m, 1H) 7.83 (t, 1H) 7.41 (s, 6H) 5.15 (s, 2H) 4.23 (q, 2H) 4.12 (d, 2H) 1.23 (t, 3H)	357	$C_{17}H_{19}N_5O_4$	57.14 57.41	5.36 5.55	19.60 19.61
2-pyridyl-*N*-oxide	**5e**	185-185.5	47	10.73 (s, 1H) 8.15 (m, 5H) 7.36 (s, 5H) 5.06 (s, 2H) 4.21 (q, 2H) 4.07 (d, 2H) 1.26 (t, 3H)	372	$C_{18}H_{20}N_4O_5$	58.06 58.07	5.41 5.41	15.05 15.04

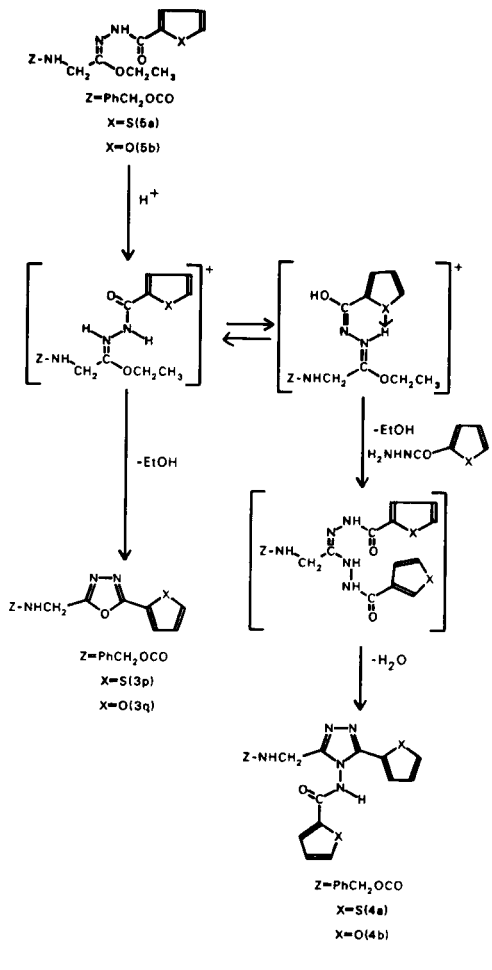
Table 6



Ar	No.	Mp °C	Yield (%)	^{1}H NMR δ, ppm d_6 DMSO		Mass Spectra m/e	Empirical Formula	Analyses (%) Calcd./Found C	H	N
2-thienyl	**3p**	155	54	8.13 (t, 1H) 7.92 (d, 1H) 7.37 (s, 5H) 4.55 (d, 2H)	8.00 (d, 1H) 7.77 (q, 1H) 5.12 (s, 2H)	315	$C_{15}H_{13}N_3O_3S$	57.13 57.14	4.16 4.18	13.32 13.31
2-furyl	**3q**	112	47	7.93 (m, 2H) 6.67 (q, 1H) 4.50 (d, 2H)	7.28 (m, 6H) 5.05 (s, 2H)	299	$C_{15}H_{13}N_3O_4$	60.20 60.15	4.38 4.41	14.04 14.03
2-pyridyl	**3r**	143	75	8.17 (m, 5H) 5.08 (s, 2H)	7.35 (s, 5H) 4.60 (d, 2H)	310	$C_{16}H_{14}N_4O_3$	60.93 60.85	4.55 4.56	18.06 17.69
2-pyrazinyl	**3s**	117-118	85	9.35 (s, 1H) 8.13 (t, 1H) 5.03 (s, 2H)	8.87 (s, 2H) 7.32 (s, 5H) 4.53 (d, 2H)	311	$C_{15}H_{13}N_5O_3$	57.88 57.74	4.21 4.23	22.50 22.44

ing when a heteroatom is present in the ring. This stabilization will occur most adventitiously when the hydrazide possesses a heteroatom specifically *beta* to the carboxyl carbon. The hydrogen-bound form of the imidate assists in triazole formation by first moving the carboxylate oxygen out of position for cyclization while maintaining an activated form of the imidate which is still open to nucleophilic attack by a second equivalent of hydrazide. This model is represented graphically for the five-membered heterocyclic series in Scheme 4. Presumably, an equilibrium is set up in solution under the reaction conditions between these two forms of the imidate. The non-stabilized intermediate is still free to form oxadiazole. One would expect that the thermodynamics of this stabilization would control the reaction course. The trends in product distribution observed for the systems studied to date tend to support such a hypothesis. That is, the relative amounts of 4-aminotriazole product should be directly correlatable with the donor capability of the ring heteroatom. Thus, it is not surprising to find that the most efficient conversions to 4-aminotriazole products are observed in systems bearing a *beta* nitrogen atom donor, *i.e.*, with 2-pyridyl and 2-pyrazinyl acid hydrazides.

SCHEME 4

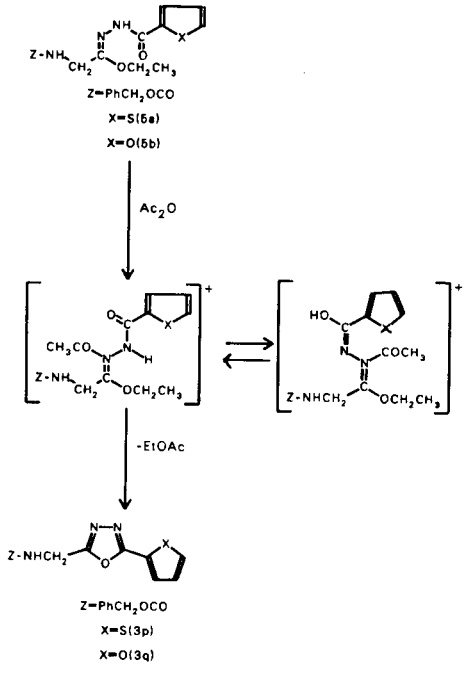


This model is also consistent with the products obtained from heating the imidates in acetic anhydride (Scheme 5). Under such conditions, the key imino protonation step is replaced by an acetylation reaction. Any hydrogen bonding by the *beta* heteroatom is completely disrupted in this acetylated intermediate. Essentially no other interaction would be expected to occur between the ring heteroatom

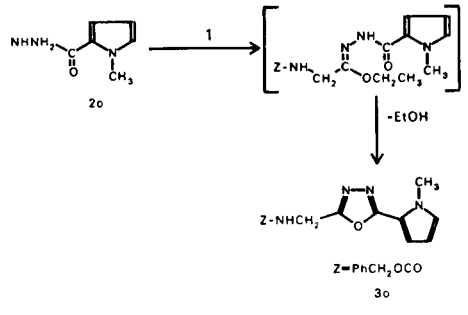
and the *N*-acetyl group. Consequently, the carboxylate oxygen is readily available for intramolecular cyclization. One would therefore anticipate that a relatively clean transformation to the oxadiazole product would occur under these conditions, and, indeed, this is the observed result.

With this model in hand, we sought to identify several chemical tests that could strengthen this hypothesis. One would expect that any steric congestion about the *beta* heteroatom would impede hydrogen bonding. This then should lead to increased oxadiazole formation by making the carboxylate oxygen more available for cyclization. Indeed, we observed that treatment of thionoester **1** with one equivalent of *N*-methylpyrrole-2-carboxylic acid hydrazide (**2o**) [14] produced the oxadiazole **3o** in high yield (Scheme 6, Table 2).

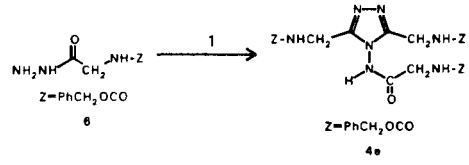
SCHEME 5



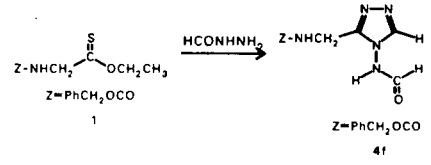
SCHEME 6



Similarly, this model predicts that other hydrazides containing a *beta* heteroatom should favor triazole formation. When thionoester **1** was treated with one equivalent of *N*-carbobenzyloxyglycine hydrazide (**6**) [15], again clean formation of an 4-aminotriazole **4e** adduct was observed. The isolated yield of this material was quite good when two equivalents of the hydrazide were employed in the reaction (Table 3).



However, this result may in part reflect a higher nucleophilic reactivity of aliphatic hydrazide derivatives since a high amount of 4-aminotriazole formation is observed between thionoester **1** and one equivalent of formyl hydrazide. Again, the yield of this triazole **4f** also increases with a stoichiometric amount of the hydrazide (Table 3).



Conclusion.

This study has confirmed that a clear and dramatic change in reaction course can take place between glycine thionoesters and heterocyclic 2-carboxylic acid hydrazides. The resulting 4-aminotriazole derivatives in many cases are formed as the major products in good yield. This approach has provided a synthetically viable and direct route to several interesting new unsymmetrically substituted 4-aminotriazole derivatives. A mechanistic rationale has been presented and tested to account for their formation. This rationale accounts for the surprisingly preferential formation of products arising from an intermolecular process rather than through intramolecular cyclization and also defines certain limits to the reaction course.

EXPERIMENTAL

Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Proton nmr spectra were recorded on a Varian EM-360 L (60 MHz) or Bruker WM-360 (360 MHz) spectrometer. The ^{13}C nmr were obtained on a Bruker WM-360 spectrometer. All proton and carbon chemical shifts are reported in ppm relative to tetramethylsilane (TMS). Chromatotron purification refers to chromatography on Harrison Research's model 7924 Chromatotron using silica gel (4 mm) plates. All solvents were Fisher reagent grade. All of the carboxylic acid hydrazides employed in this study were either obtained from commercial sources or prepared by literature procedures. Microanalyses were performed by Atlantic Microlabs, Inc.

A General Procedure for the Preparation of 5-Substituted 2-(*N*-Carbobenzyloxy)aminomethyl-1,3,4-oxadiazoles, **3a-o**, Table 2.

To a stirred solution of thionoester, **1**, (11.0 g, 0.044 mole), in 150 ml of acetonitrile was added the appropriate acid hydrazide substrate (0.040 mole). The resulting solution was then refluxed overnight (14-18 hours), cooled to room temperature, and concentrated on a rotovap to give the crude oxadiazole product as an oil. Trituration of this oil with either diethyl ether or 10% ethanol in diethyl ether caused the material to solidify. One recrystallization from ethanol or ethanol/ether was usually sufficient to give the desired products in analytically pure form (Table 2). In those cases where the product failed to crystallize, the crude oil could be conveniently purified *via* preparative tlc using a Chromatotron, and eluting with 50:50 ethyl acetate/cyclohexane.

A General Procedure for the Preparation of 3-(*N*-Carbobenzyloxy)-aminomethyl-4-amino-1,2,4-triazoles, **4a-f**, Table 3.

The following procedure is representative: To a stirred solution of the thionoester, **1**, (2.53 g, 0.01 mole) in 50 ml of acetonitrile was added thiophene-2-carboxylic acid hydrazide (2.84 g, 0.02 mole). The resulting solution was heated at reflux for 18 hours, and then was cooled to room temperature. A solid precipitate formed which was collected by filtration, washed with ether and air-dried to give a gray solid. One recrystallization from ethanol gave **4a** as an off-white solid, 2.0 g (46%), mp 222-224°. Mass spectra, nmr data and elemental analyses were all consistent with pure products (Table 3).

A General Procedure for the Preparation of the Imidates, **5a-e**, Table 5.

The following procedure is representative: A stirred solution of the thionoester, **1**, (25.6 g, 0.10 mole) in 75 ml of ethanol was cooled to -40°. Then thiophene-2-carboxylic acid hydrazide (14.2 g, 0.10 mole) was added as a solid. The resulting mixture was stirred at -40° for 6 hours and then warmed slowly to room temperature overnight. The hydrazide slowly dissolved, then a new precipitate formed. This precipitate was collected by filtration, washed with ether and air-dried to give **5a** as a beige solid, 21.3 g (59%), mp 144°. Mass spectra, nmr data and elemental analyses were all consistent with pure product (Table 5).

A General Procedure for Cyclization of Imidates **5a-e** to the Corresponding Oxadiazoles **3p-s**, Table 6.

The following procedure is representative: A stirred solution of the imidate, **5a**, (7.2 g, 0.02 mole) in 75 ml of acetic anhydride was heated at reflux for 48 hours, at which time tlc indicated the complete consumption of the imidate starting material. The solution was cooled to room temperature and concentrated *in vacuo* to give a light brown precipitate. This solid was then recrystallized from ethyl acetate to give the desired oxadiazole **3p** as a white solid, 3.4 g (54%), mp 155°. Mass spectra, nmr-data and elemental analyses were all consistent with pure product.

Acknowledgement.

The authors wish to thank Dr. Michael R. Thompson of the Corporate Research Laboratories of Monsanto Company for his solution of the x-ray structure of **4a**.

Supplementary Material.

Tables of atomic positional parameters, thermal parameters, *etc.* for **4a** are available from the authors.

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