Novel Cyclization Reactions of Mono- and Dichloroazodienes. A New Synthesis of Substituted Pyridazines [a]

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Cyclization of the *in-situ* generated chloroazodienes with a variety of enamines was found to give chloro-substituted tetrahydropyridazines which could be aromatized to pyridazines by base treatment. This sequence appears to be a formal 4 + 2 hetero Diels-Alder reaction with a high degree of regio and stereo control and constitutes a new synthesis of substituted pyridazines. However, cyclization of the corresponding dichloroazodienes with acyclic enamines gave not only the expected pyridazine product, but also gave an *N*-aminopyrrole product. Combination of the dichloroazodiene with cyclic enamines gave bicyclic dihydropyridazines, bicyclic pyridazines, and acyclic enamines which could be forced to close to the bicyclic dihydropyridazines upon further heating. These results would indicate a stepwise mechanism. The scope and mechanistic speculations on these reactions will be presented.

While exploring the novel cyclization reactions of 4-chloroazodienes with electron rich olefins we developed a new and general synthesis of substituted 3-phenypyridazines. A number of these analogs were found to exhibit bleaching herbicidal activity (phytoene desaturase inhibition). Further methodology development coupled with analog synthesis led to the preparation of 3-heteroaryloxy and 3-aryloxypyridazines with increased unit activity and selectivity as well as good environmental properties. These compounds were found to be more active than current commercial standards on a number of important weed species with selectivity in corn in the US and small grains in Europe. Greenhouse activity of the most active analogs ranged from 17-140 g/hectare on important narrow-leaf species.

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Introduction.

A number of reports have appeared describing the generation and reactions of non-halogenated azodienes with electron rich olefins [1-9]. These reactions lead mainly to the 6-membered tetrahydropyridazine products or to the 5-membered *N*-aminopyrrole products and are formal 4 + 2 or 3 + 2 cyclizations of an azodiene with an olefin. Derivatives prepared in this fashion are not set up for conversion directly to the corresponding aromatized pyridazines unless an external oxidant or strong base is utilized which limits their utility for the preparation of these compounds. Previous attempts to introduce a labile group into the tetrahydropyridazine followed by an aromatization to give pyridazines are described, but these reactions are limited in scope [1,10,11]. Also, extensively studied are the addition of active methylene compounds to non-halogenated azodienes followed by cyclization and elimination of water to give *N*-aminopyrroles [12]. However, this sequence is not useful for the synthesis of pyridazines. We have an interest in 3-substituted pyridazines due to their unique biological activity [13] and sought to develop a new and general synthesis of these molecules. We envisioned introducing a labile group into the tetrahydropyridazine from a 4-haloazodiene [14,15]. This labile halogen could then be eliminated to produce the aromatized pyridazine providing that the other groups on the tetrahydropyridazine were stable to the reaction conditions.

We wish to report here a new and general procedure for the preparation of pyridazines that relies on the cyclization of a 1-carboxyethyl-3-phenyl-4-haloazodiene with an electron rich olefin and a subsequent aromatization with a base [16]. These haloazodiene cyclizations are best characterized as inverse electron demand, 4 + 2 hetero Diels-Alder reactions that maintain a high degree of regio- and stereochemical control. Unlike the precedented syntheses of the pyridazine ring [17], the azodiene route allows for the incorporation of many different types of functional groups. The sequence of a haloazodiene cyclization to a halotetrahydropyridazine followed by an aromatization reaction constitutes a new and general synthesis of substituted pyridazines.

Also reported, and in contrast to the 4-haloazodiene cyclizations described above, are the novel cyclization reactions of 1-carboxyethyl-3-phenyl-4,4-dichloroazodienes which yield mixtures of products [18]. *N*-aminopyrroles, pyridazines, a dihydropyridazine and non-cyclized enamine intermediate are obtained from these dichloroazodiene cyclizations depending on the electron rich olefin that is used. These results suggest a stepwise addition of the electron rich olefin to the dichloroazodiene. No reports of successful cyclization reaction with dichloroazodienes have appeared, however several authors mention the preparation and addition elimination reactions of these compounds [19].

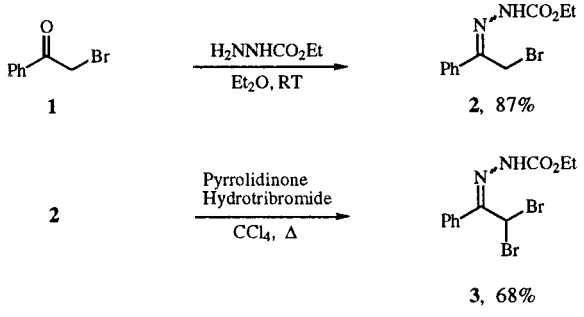
[a] Plenary lecture at the Sixth International Symposium on the Chemistry and Pharmacology of Pyridazines, Clearwater Beach, FL November 4-7, 1998.

Pyridazine Chemistry.

Synthesis and Reactions of Monohaloazodienes.

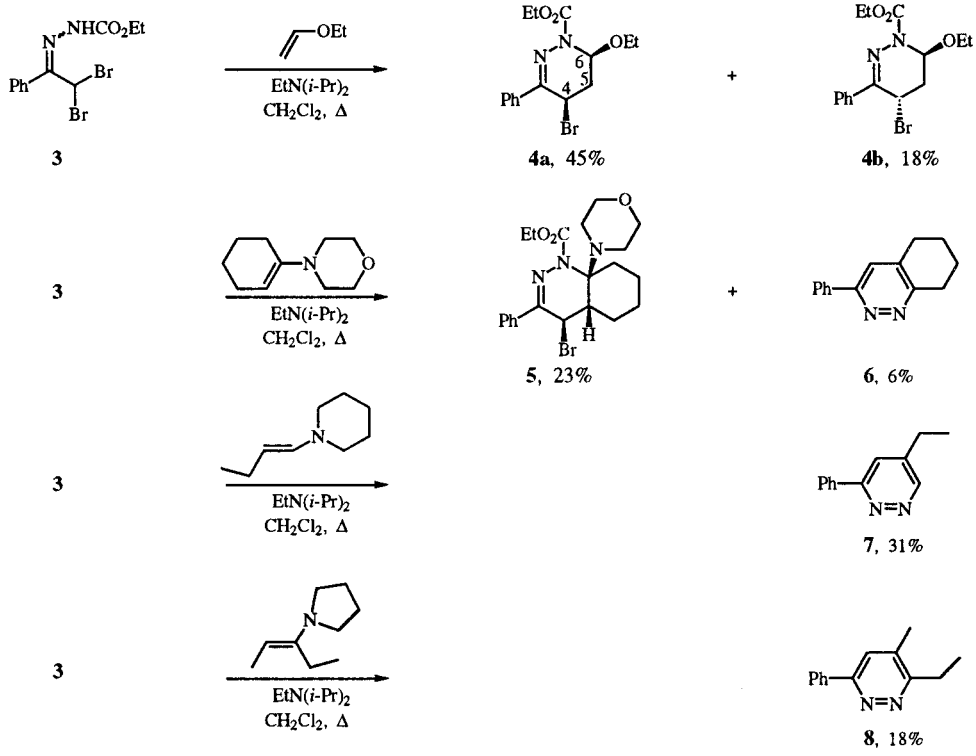
The first step in developing a viable route to pyridazines required the preparation of a dihalohydrazone. Our initial attempts centered around the preparation of dibromohyrazone **3**, Scheme 1. Treatment of 2-bromoacetophenone with ethyl carbazate gave **2** in 87% yield. Further bromination of **2** with pyrrolidinone hydrotribromide gave the dibromohydrazone **3** in 68% yield. This material served as the precursor to a bromo-substituted azodiene upon treatment with base.

Scheme 1



The azodiene was usually generated *in-situ* from the dibromohydrazone by treatment with a hindered base such as Hünig's base. Treatment of **3** with Hünig's base in refluxing dichloromethane produced a deep red color of the bromoazodiene which was discharged in the presence of the electron rich olefin [20] indicating that the reaction had taken place. Combination of the azodiene derived from **3** with ethyl vinyl ether gave the *cis*-tetrahydropyridazine **4a** in 45% yield and the *trans*-tetrahydropyridazine **4b** in 18% yield, Scheme 2. Reaction of the morpholine enamine of cyclohexanone with the azodiene generated from **3** gave a mixture of diastereomers which was not stable at RT after isolation. One compound crystallized from this mixture in 23% yield which was the *cis*-isomer **5**. The pyridazine **6** was also isolated from this reaction in 6% yield. Treatment of **3** with Hünig's base followed by the enamines of either butanal or 3-pentanone gave the pyridazine products **7** in 31% yield and **8** in 18% yield. None of the tetrahydropyridazine products were isolated from these reactions. Apparently the bromotetrahydropyridazines were not stable under the reaction conditions in some cases and were aromatized directly to the pyridazine products.

Scheme 2



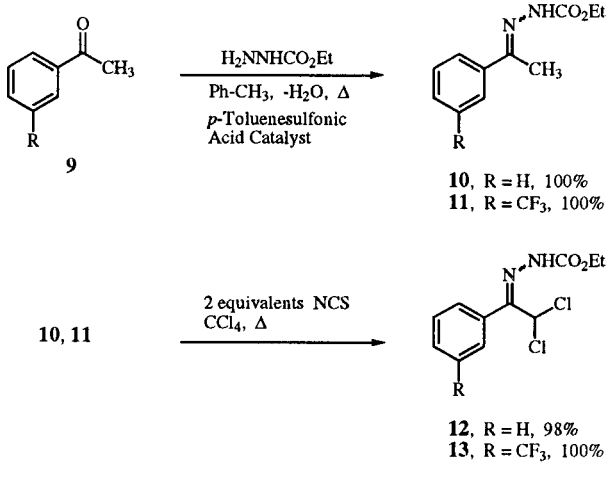
In systems such as the disubstituted tetrahydropyridazines **4a** and **4b**, the group at the 6-position is in an axial position allowing the molecule to adopt a half-chair conformation [2]. The stereochemical assignments for **4a** and **4b** could then be made based on the differences in coupling constants for the H-4 proton. The equatorial proton H-4 of compound **4a** is a d which appears at δ 5.01 (400 MHz nmr spectrum) and has a 6.0 Hz coupling to the axial proton H-5. The axial proton H-4 of compound **4b** is a dd which appears at δ 5.24 and has a 15.0 Hz coupling to the axial H-5 proton and a 8.0 Hz coupling to the equatorial H-5 proton. The large di-axial coupling constant of 15.0 Hz for compound **4b** is what distinguishes the *trans*-isomer **4b** from the *cis*-isomer **4a**. This phenomenon has proven to be general for all of the 4,6-disubstituted tetrahydropyridazines that we have prepared and is consistent with what is reported for related systems [2].

At this point we elected to prepare the dichlorohalohydrazones as starting materials for the azodiene reaction in hope of generating stable tetrahydropyridazine intermediates that could be isolated and studied. We found that high yields of dichlorohydrazones **12** and **13** were obtained from the acetophenones **9** by treatment with ethyl carbazate followed by two equivalents of *N*-chlorosuccinimide, Scheme 3. The dichlorohydrazones usually existed as a mixture of *E* and *Z* isomers. When hydrazone **13** was treated with Hünig's base in an nmr tube, the solution turned deep red and gave what was presumed to be a 10:1 mixture of the *E*-azodiene to the *Z*-azodiene as shown in Equation 1. The 400 MHz nmr signal for the olefinic proton of the *E*-isomer was at 7.60 ppm while the *Z*-isomer was at 6.84 ppm. One would expect the proton of the Z-isomer to be at higher field since it is in the shielding region of the phenyl ring [14]. The next step was to study the reaction of the 4-chloroazodienes with electron rich olefins.

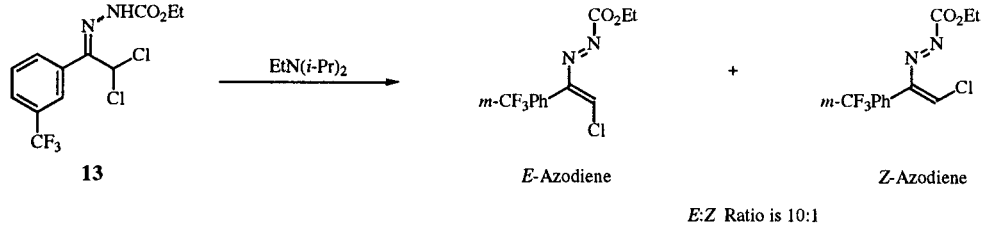
The dichlorohydrazones **12** and **13** were treated with Hünig's base to generate the 4-chloroazodiene *in-situ*, which, in the presence of a variety of electron rich olefins [20], react to afford the tetrahydropyridazine adducts, Table 1. These sequences were found to usually give two diastereomers of the corresponding tetrahydropyridazine or in some cases the pyridazines directly from the reaction mixture. A subsequent aromatization of the tetrahydropyridazines with a base gave the corresponding pyridazines in high yields.

Combination of the chloroazodiene derived from **12** with ethyl vinyl ether gave two diastereomers of the corresponding tetrabydropyridazines in good yield, entry 1, Table 1. These diastereomers were assigned based on the vicinal coupling constants in the proton nmr as discussed above. Compounds **14a** and **15a** were converted to the 3-phenyl substituted pyridazine **16** in 95% yield using potassium hydroxide in ethanol. In an analogous fashion, the *m*-trifluoromethylphenylpyridazine **16b** was prepared without isolation of the corresponding tetrahydropyridazines in 50% overall yield from the dichlorohydrazone, entry 2, Table 1. This reaction was also successful with other enol ethers such as *trans*-3-ethoxy-2-propene, entries 7 and 8, Table 1, which gave two diastereomers of the corresponding trisubstituted pyridazines in good yields. An explanation of the structure determination relative to the nmr data for the 4,5,6-trisubstituted tetrahydropyridazines is given for Scheme 5 below. The diastereomers in entries 7 and 8 of Table 1 were aromatized in good yield to the corresponding 5-methyl substituted pyridazines **16g** and **16h**. Combination of 2-methoxypropene with the chloroazodienes gave the 6-methyl substituted pyridazines **16p** and **16q** directly from the reaction mixture without further base treatment, entries 16 and 17, Table 1. The yields of the products derived from 1,1-disub-

Scheme 3



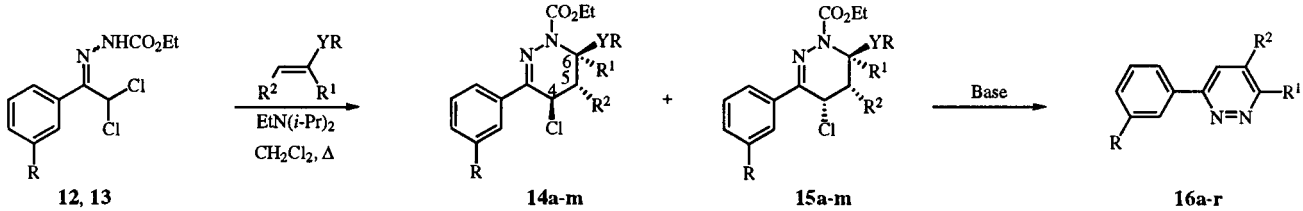
Equation 1



E:*Z* Ratio is 10:1

Table 1

Synthesis of Tetrahydropyridazines **14** and **15** and Pyridazines **16** *Via* Chloroazodienes [a]



12, 13 **14a-m** **15a-m** **16a-r**

Entry	R	YR	R^1	R^2	% Yield 14	% Yield 15	% Yield 16
1	H	OEt	H	H	**a**, 69	**a**, 10	**a**, 95 [b]
2	CF_3	OEt	H	H	-[c]	-[c]	**b**, 50 [b]
3	H	Morpholino	$-(CH_2)_4-$	$R^1 = R^2$	**c**, 34	-[e]	**c** (**6**), 92 [d]
4	H	Morpholino	$-(CH_2)_3-$	$R^1 = R^2$	-[e]	-[e]	**d**, 25 [f]
5	H	Piperidino	H	Et	**e**, 45 [g]	**e**, 22 [g]	**e** (**7**), 34 [d]
6	CF_3	Piperidino	H	Et	**f**, 35 [g]	**f**, 17 [g]	**f**, 33 [h]
7	H	OEt	H	Me	**g**, 66	**g**, 26	**g**, 68 [b]
8	CF_3	OEt	H	Me	**h**, 40	**h**, 14	**h**, 76 [h]
9	CF_3	Morpholino	H	Ph	**i**, 46	**i**, 39	**i**, 82 [b]
10	CF_3	Morpholino	H	*m*-CF_3Ph	-[c]	-[c]	**j**, 43 [b]
11	CF_3	Morpholino	H	*i*-Pr	**k**, 65	**k**, 10	**k**, 38 [b]
12	CF_3	Morpholino	H	CF_3	**l**, 25	**l**, 17	**l**, 85 [b]
13	H	Morpholino	H	CF_3	**m**, 54	**m**, 15	**m**, 51 [b]
14	H	Morpholino	Et	Me	-[c]	-[c]	**n** (**8**), 22 [d]
15	CF_3	Morpholino	Me	Et	-[c]	-[c]	**o**, 12 [b]
16	H	OMe	Me	H	-[e]	-[e]	**p**, 13 [f]
17	CF_3	OMe	Me	H	-[e]	-[e]	**q**, 21 [f]
18	CF_3	Morpholino	Me	CO_2Et	-[c]	-[c]	**r**, 22 [b,i]

[a] The reactions were run with 5 equivalents of enol ether or 1.1-2.5 equivalents of eneamine in refluxing dichloromethane for 4-24 hours with equal amounts of Hünig's base present in the reaction mixture; [b] Potassium hydroxide in ethanol was used for the aromatization reaction; [c] After workup, the tetrahydropyridazine intermediates were used directly in the aromatization reaction and were not isolated; [d] Potassium *t*-butoxide in *t*-butyl alcohol was used for the aromatization reaction; [e] This isomer was not observed; [f] The pyridazine was isolated directly from the reaction of the azodiene with the electron rich olefin; [g] Isolated as a 2:1 mixture of diastereomers **14**:**15**; [h] Sodium hydroxide in dimethyl sulfoxide/water was used for the aromatization reaction; [i] The pyridazine was isolated as the carboxylic acid after treatment of the reaction with base.

stituted olefins were somewhat lower than the 1,2-disubstituted olefins. This phenomenon has proven to be general for the electron rich olefins that we have studied to date and may be related to steric hindrance in the transition state of the 4 + 2 reaction.

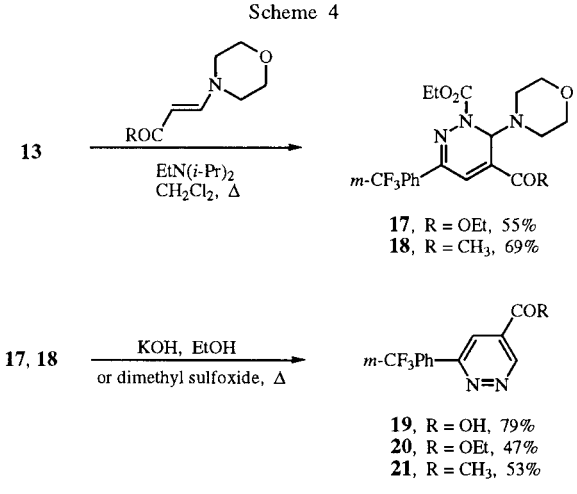
The chloroazodienes also combined smoothly with enamines to give the corresponding tetrahydropyridazines. The cyclic morpholine enamine of cyclohexanone gave **14c**, entry 3, Table 1, which had the all *cis* stereochemistry. Compound **14c** was aromatized to the bicyclic pyridazine **16c** with base in high yield. The cyclic enamine of cyclopentanone gave the pyridazine **16d** in moderate yield directly from the azodiene reaction, entry 4, Table 1. The *trans*-disubstituted enamines in entries 5, 6, 9, 10, 11, 12, and 13 of Table 1 all gave two diastereomers of the corresponding tetrahydropyridazines in good yield. All were converted to the pyridazines in good yields by base treatment. In the cases of the trisubstituted enamines in entries 14, 15, and 18 a significant amount of aromatized product was obtained directly from the azodiene reaction. However, in lieu of attempting to separate these mixtures, the crude materials were treated with base to complete any aromatizations followed by purification to give the pyridazines shown in moderate yields.

In general, the azodiene route to tetrahydropyridazines and subsequent aromatization to pyridazines is compatible with either enol ethers or enamines that are substituted with a variety of functional groups. The mono- and di-substituted olefins gave higher yields of cyclization products than the tri-substituted olefins. This may be due to steric hindrance in the 4 + 2 reaction. A number of olefins did not give any cyclization products in these reactions. These include: *cis*-1-ethoxy-2-bromoethylene, 1-methoxy-1-buten-3-yne, ethyl *trans*-3-ethoxyacrylate, 1-methoxy-2-phenylethylene, ethyl 3-morpholino-4,4,4-trifluoroacrylate, and 3-(*t*-butyldimethylsilyloxy)-2-pentene.

In these cases, the olefin may not be electron rich enough to undergo cyclization with the chloroazodienes or sterics may also play a role.

The reaction of the azodiene derived from **13** with a 1,2-disubstituted enamine where the 2-position was substituted with a carbonyl group resulted in the formation of yellow dihydropyridazine products **17** and **18** rather than the tetrahydropyridazine products described above, Scheme 4. These products result from the base induced elimination of hydrogen chloride from the molecule. The dihydropyridazine **17** could be aromatized with a base to give the carboxylic acid **19**. The ester and ketone **20** and **21** were formed simply by heating in a high boiling solvent.

Scheme 4



In the reactions of chloroazodienes described above all of the disubstituted olefins had the *trans* geometry about the double bond. One reaction was run where the olefin was a mixture of *cis*- and *trans* isomers in an effort to understand the sterochemistry of the chloroazodiene cyclization reaction. There are four diastereomeric tetrahydropyridazines that are possible from the azodiene reaction shown in Scheme 5 if a regiospecific, concerted, 4 + 2 Diels-Alder reaction is in operation. Combination of the chloroazodiene **13** with the enamine of methoxyacetaldehyde (1.17:1.00 mixture of *cis* and *trans* isomers) gave three out of four possible diastereomeric tetrahydropyridazines, Scheme 5. Compound **22** was obtained in 25% yield, **23** was obtained in 20% yield, and **24** was obtained in 16% yield.

As described above, the morpholine prefers to be in an axial position which allows the tetrahydropyridazine to adopt a half-chair conformation [2]. Using this premise, the minimum energy conformations were calculated using the Sybil program for all four of the possible diastereomers shown in Scheme 5. These energy minimized structures were then transferred to the Macromodel program and values were calculated for the vicinal proton-proton nmr coupling constants, Table 2. The calculated vicinal coupling constants were then compared with the actual values that are shown in Table 2.

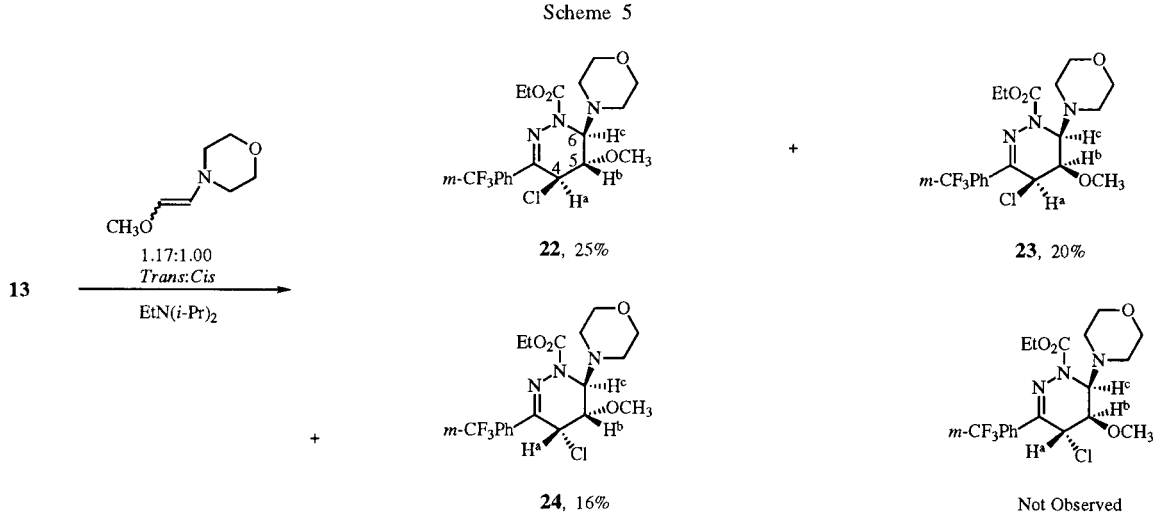
Table 2

400 MHz ^{1}H NMR Coupling Constants for Compounds **22**, **23**, and **24** [a]

Compound	$^3J_{a,b}$ Obs.	$^3J_{a,b}$ Calcd.	$^3J_{b,c}$ Obs.	$^3J_{b,c}$ Calcd.	$^4J_{a,c}$ Obs.
22	1.44	2.2	2.64	2.7	1.36
23	5.42	4.0	3.28	3.3	1.00
24	4.58	3.5	4.58	3.5	0

[a] All nmr spectra were taken in deuteriochloroform and coupling constants are shown in Hz. See experimental section for complete nmr data. Calculated three bond coupling constants were derived using the Macromodel® program. Four bond couplings were not calculated.

Scheme 5



One of the four possible diastereomers was eliminated from consideration since it was calculated to have a large di-axial coupling of 7.3 Hz between the 4-H axial proton Ha and the 5-H axial proton Hb, Scheme 5 (structure labeled "not observed"). None of the three diastereomers isolated from the azodiene reaction had a large di-axial coupling of this magnitude between the 4-H and 5-H protons. There were several distinguishing characteristics in the proton nmr's of the three remaining isomers that allowed for the assignment of the stereochemistry shown in Scheme 5.

The 4-H equatorial proton of **22** (Scheme 5, Table 2) was observed at δ 4.61 and was a dd with coupling constants of 1.44 and 1.36 Hz. The 1.44 Hz coupling is between the 4-H equatorial proton Ha and the 5-H equatorial proton Hb. The 1.36 Hz coupling is between the 4-H equatorial proton Ha and the 6-H equatorial proton Hc. This latter coupling is a W-coupling that is only possible when **22** adopts a half-chair conformation with the morpholine and chloro groups both in an axial position. Also, the methoxy group of this isomer must be in an axial position *(trans* to the morpholine) since the coupling between the 4-H and 5-H protons is small at 1.44 Hz which indicates a di-equatorial relationship.

The 4-H equatorial proton Ha of **23** (Scheme 5, Table 2) has a shift at δ 5.06 and is a dd with a coupling of 5.42 Hz to the 5-H axial proton Hb and a W-coupling of 1.00 Hz to the 6-H equatorial proton Hc. As was shown above with **22** the presence of the W-coupling in **23** indicates that this isomer is also in a half-chair conformation with the morpholine and the chloro groups both in axial positions. Since the coupling between the 4-H and 5-H protons of **23** is 5.42 Hz (this is a larger coupling than the equatorial-equatorial coupling of 1.44 Hz between the 4-H and 5-H protons of **22**), this indicates an equatorial-axial relationship between Ha and Hb. This places the 5-methoxy group in an equatorial position *cis* to the morpholine in an axial position.

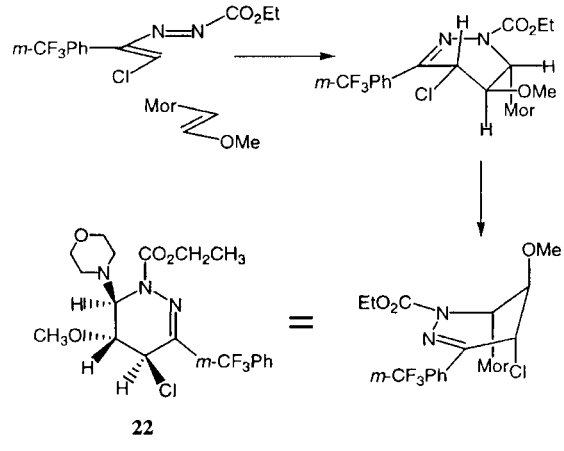
In the case of **24** (Scheme 5, Table 2) the 4-H proton Ha is a doublet with a 4.58 Hz coupling to the 5-H equatorial proton Hb. No W-coupling was observed for this compound. These coupling constants indicate that **24** is in a half-chair conformation with the chlorine in an equatorial position. The methoxy is in an axial position *trans* to the axial morpholine. The absence of the W-coupling confirms this.

The calculated values for the vicinal coupling constants (Table 2) of the diastereomers shown in Scheme 5 are close to the values that were observed experimentally. These data further corroborate the structural assignments as discussed above.

In all of the reactions of the chloroazodienes reported in Table 1 above, only two diastereomers were observed from the reaction. In every case, the nmr data for the diastereomers in Table 1 was consistent with what was observed for **22** and **23** in Scheme 5. All of the stereochemical assignments in Table 1 are corroborated based on this analogy. The pure tetrahydropyridazine isomers were found to be stable under the reaction conditions used for the azodiene cyclization and were not interconvertible.

The results of the chloroazodiene cyclizations are best explained based on a regiospecific, concerted, 4 + 2 Diels-Alder reaction with a high degree of *endo* character. As mentioned above, the chloroazodiene is a 10:1 mixture of *E* and *Z* isomers, therefore the *E*-isomer is the major contributor in the reaction. The stereochemistry of the olefin is retained in the products. One of the preferred modes of reaction is shown in Scheme 6. Here the *trans*

Scheme 6



22

olefin is reacting *via* an *endo* transition state with respect to the morpholine with the *E*-azodiene to give after a ring flip compound **22**, Scheme 6. This mode of reaction would also lead to the major diasteromers **14** shown in Table 1. Reaction of the *trans* olefin *via* an *endo* transition state (not shown) with respect to the methoxy group with the *E*-azodiene would give compound **23** (Scheme 5) and the minor diastereomers **15** shown in Table 1. When a *cis* olefin is also present as in Scheme 5 the preferred mode of reaction is an *endo* transition state (not shown) with respect to the morpholine and the methoxy substituents with the *E*-azodiene to give compound **24**. Similar arguments may be made for the Z-isomer of the chloroazodiene to give the same products in Scheme 5, but this isomer of the azodiene is probably not a major contributor to the product mixture.

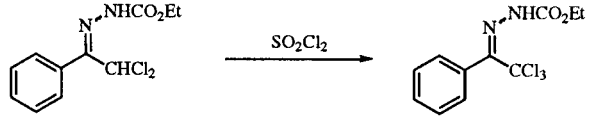
Synthesis and Reactions of Dichloroazodienes.

The methodology described above for the synthesis of pyridazines from chloroazodienes was extended to include the synthesis and reactions of the *in-situ* generated

1-carboxyethyl-3-phenyl-4,4-dichloroazodiene. Cyclization reactions of this dichloroazodiene are not only in the correct oxidation state for aromatization directly to pyridazines, but also allow for the introduction of a chloro group into the molecule. In contrast to the reactions described above, the dichloroazodiene cyclizations yield mixtures of products. *N*-aminopyrroles, pyridazines, a dihydropyridazine and/or non-cyclized enamine intermediates are isolated from the cyclization reactions depending on the electron rich olefin that is used. These results suggest that a stepwise mechanism may be preferred in the cyclization reactions of the dichloroazodiene rather than a concerted 4 + 2 Diels-Alder.

The preparation of the trichlorohydrazone precursor necessary for the dichloroazodiene formation is shown in Equation 2. The trichlorohydrazone is prepared from dichlorohydrazone **12** by using neat sulfuryl chloride to give trichlorohydrazone **25** in 85% yield. The highly colored dichloroazodiene is generated *in-situ* in the presence of the electron rich olefin [20] from the trichlorohydrazone **25** by treatment with Hünig's base in methylene chloride at RT to reflux or in carbon tetrachloride at reflux to give the products shown in Tables 3 and 4.

Equation 2



12 **25**, 85%

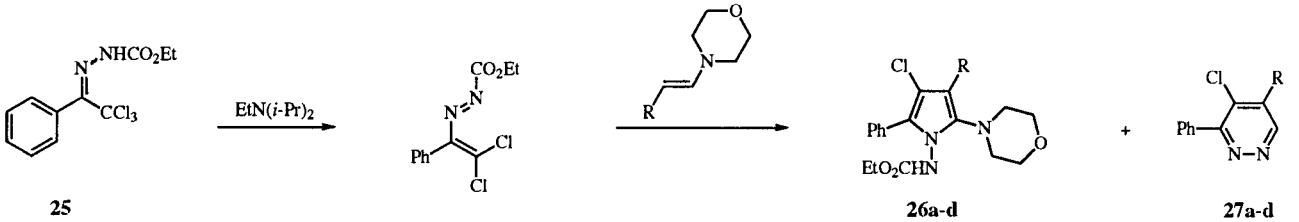
When the enamine contains a mono-substituted alkyl group as in Table 3 the products obtained from the dichloroazodiene cyclization are both the *N*-aminopyrroles **26a** and **26c** and the pyridazines **27a** and **27c** in roughly equal amounts. When the enamine was substituted with a phenyl group the main product (75%) was the *N*-aminopyrrole **26d** and the minor product was the pyridazine **27d**. The methoxy-substituted enamine gave only the *N*-aminopyrrole product **26b**.

A similar set of products were obtained under the same reaction conditions when cyclic or disubstituted enamines were utilized in the reaction with the dichloroazodiene, Table 4.

Combination of the morpholinocyclopentene with the dichloroazodiene gave only the chloropyridazine product **28** in 48% yield. The reaction with morpholinocyclohexene gave a small amount (9%) of the chloropyridazine **30** as well as an unusual bicyclic *N*-carboxyl substituted pyridazine (44%) derivative **29** that appears to have been formed by a ring closure reaction followed by a morpholine elimination. Morpholine elimination products were also obtained in the reactions of morpholinocycloheptene and morpholinocyclooctene. However, in these cases the *N*-aminopyrroles were formed and the double bond migrated away from the bridge head to give the products **31** and **34**. The chloropyridazine **32** was present in the reaction with the morpholinocycloheptene, but not with morpholinocyclooctene. In addition to the cyclic products that were isolated from these reactions, acyclic enamine intermediates were also isolated in the case of compounds **33** and **35**. The structural assignments in Tables 3 and 4 were made primarily on the basis of ^{1}H nmr and APT nmr data.

Table 3

Synthesis of Chloro-Substituted *N*-Aminopyrroles **26** and Pyridazines **27**

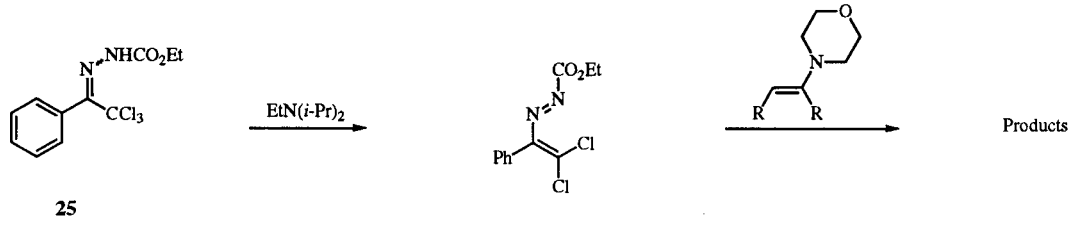


25 **26a-d** **27a-d**

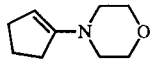
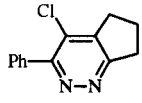
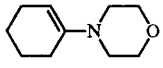
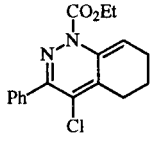
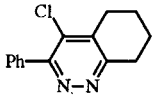
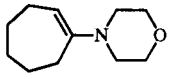
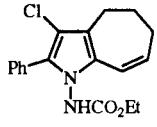
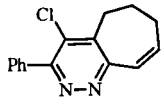
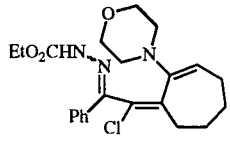
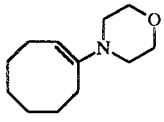
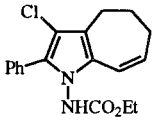
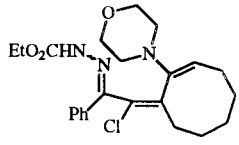
Entry	R	% Yield **26**	% Yield **27**
1 [a]	Et	**a**, 15	**a**, 16
2 [a]	OCH_3	**b**, 11	----
3 [b]	*i*-Pr	**c**, 23	**c**, 36
4 [b]	Ph	**d**, 75	**d**, 7

[a] Reaction was performed at room temperature in dichloromethane with 2.0 equivalents of Hünig's base and 1.6-3.3 equivalents of the olefin for 2.5-6 hours; [b] Reaction was performed in dichloromethane at reflux with 2.0 equivalents of Hünig's base and 2.5-3.3 equivalents of olefin for 18-24 hours.

Table 4
Reactions of Cyclic Enamines with Dichloroazodienes



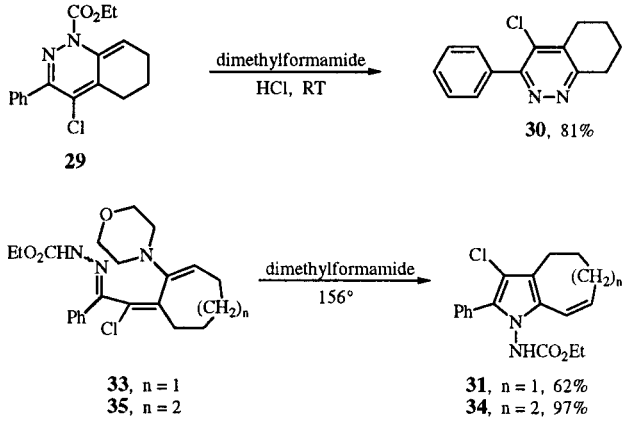
25

Entry	Enamine		Products	
1 [a]		-	 **28**, 48%	-
2 [a]		 **29**, 44%	 **30**, 9%	-
3 [a]		 **31**, 36%	 **32**, 12%	 **33**, 31%
4 [b]		 **34**, 3%	-	 **35**, 31%

[a] Reaction was performed at reflux in dichloromethane with 2.0 equivalents of Hünig's base and 1.3-1.8 equivalents of the olefin for 1.5-4 hours; [b] Reaction was performed in carbon tetrachloride at reflux with 2.0 equivalents of Hünig's base and 2.6 equivalents of olefin for 24 hours.

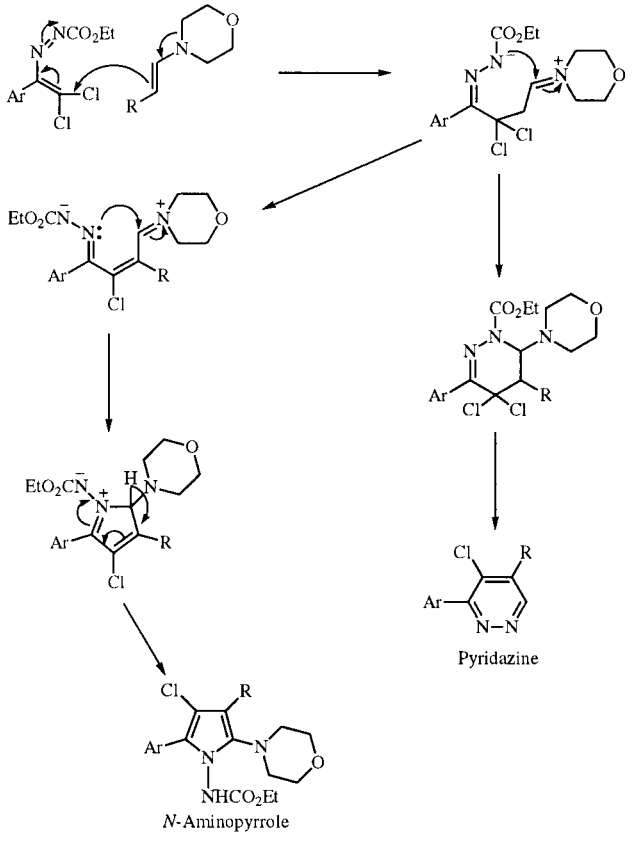
It appeared that in entries 2-4, Table 4, that there were compounds isolated that were precursors to the other products isolated. In an effort to test this hypothesis these compounds were subjected to more stringent reaction conditions, Scheme 7. When compound **29** was treated with acid in *N,N*-dimethylformamide at RT the pyridazine **30** was formed in 81% yield. Simply heating the open chain compounds **33** and **35** in *N,N*-dimethylformamide at 156° resulted in the formation of cyclic *N*-aminopyrroles **31** (62% yield) and **34** (97% yield) respectively. These experiments suggest that **29** was an intermediate in the formation of **30** and that **33** and **35** were precursors to **31** and **34**.

Scheme 7



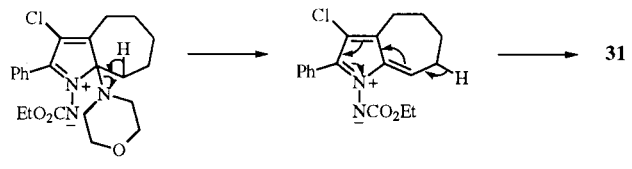
A stepwise mechanism that explains the results obtained in Tables 3 and 4 is shown in Scheme 8. Stepwise addition of the enamine to the dichloroazodiene leads to a zwitterionic intermediate. Cyclization of the anion on the nitrogen alpha to the carboxylate would lead to the 6-membered tetrahydropyridazine, which upon aromatization yields a chloropyridazine [21]. Alternatively, cyclization using the lone pair on the nitrogen beta to the carboxylate would lead to a 5-membered zwitterion which upon rearrangement would yield the *N*-aminopyrrole.

Scheme 8



When cyclic enamines are used the reaction probably proceeds through the intermediate shown in Equation 3. Here the cyclic 5-membered ring intermediate cannot lose a proton to give the aromatized *N*-aminopyrrole directly. Morpholine elimination would give a double bond at the bridgehead which then rearranges by loss of a proton to give the *N*-aminopyrrole **31** where the double bond is in the saturated ring.

Equation 3



In summary, the reactions of 1-carboxyethyl-3-phenyl-4-chloroazodienes with a variety of electron rich olefins produces tetrahydropyridazines with a high degree of stereochemical and regiochemical control. This indicates that these cyclizations are concerted, 4 + 2 hetero Diels-Alder reactions with a high degree of *endo* character. The chloro-substituted tetrahydropyridazines were aromatized in moderate to high yields to pyridazines. This sequence constitutes a new and general synthesis of substituted pyridazines that is superior to the methodology currently available for the preparation of these molecules. In contrast to the chloroazodiene cyclizations the synthesis and reaction chemistry of 1-carboxyethyl-3-phenyl-4,4-dichloroazodienes gives *N*-aminopyrroles, pyridazines, a dihydropyridazine and/or non-cyclized enamine intermediates depending on the substitution pattern of the electron rich olefin. It is most likely that the compounds derived from dichloroazodienes are derived by a stepwise addition of the enamine to the dichloroazodiene since such a variety of products have been isolated and shown to be interconvertable. The reactions described here are the first reported cyclization reactions for dichloroazodienes.

Pyridazine Biology.

The carotenoid biosynthetic pathway (Figure 1) has been a target for the discovery of new herbicidal agents for over 20 years. Much of this pathway is present only in the plant kingdom, which makes it attractive from a mammalian safety standpoint. Many new herbicidal agents have been investigated that inhibit certain enzymes in this pathway. In particular, the inhibition of phytoene desaturase serves as a target for many herbicide discovery programs throughout the ag industry and has recently been the topic of several reviews [22-24]. We have developed a series of pyridazine herbicides that inhibit phytoene desaturase [25] that are among the most active and selective analogs discovered to date with this mode of action [26-33]. Five of these analogs (Figure 2) have undergone extensive field testing and have exhibited selectivity in corn in the US and small grains in Europe. We refer to these compounds as azodiene heterocycle herbicides since the original synthesis of the 3-phenylpyridazine lead is derived from a novel 4 + 2 azodiene cyclization reaction.

Synthesis and Structure Activity Relationship Studies.

3-Phenylpyridazines.

Our entry into pyridazine chemistry revolved around the discovery of a novel 4 + 2 cycloaddition reaction of a haloazodiene with electron rich olefins (Figure 3). These azodiene cycloaddition reactions give rise to the synthesis of a number of heterocyclic molecules, which include tetrahydropyridazines, pyridazines, pyridazinones, *N*-aminopyrroles, pyrroles, and triazinones. The details of many

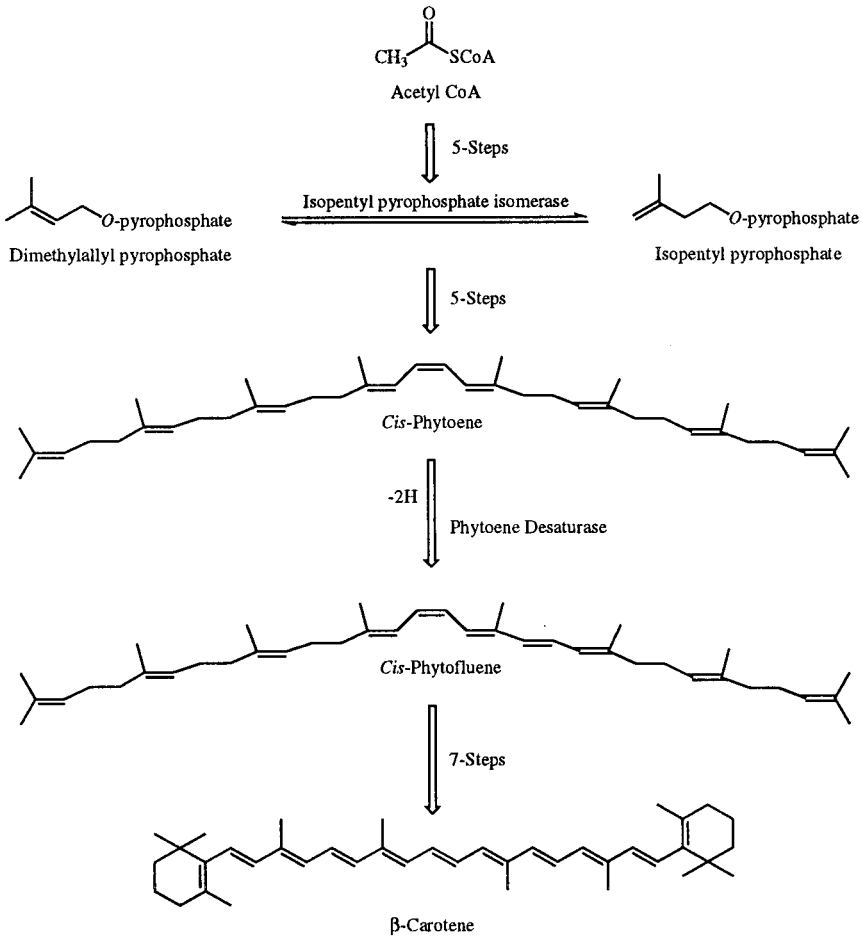
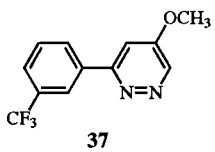
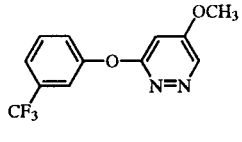


Figure 1. Carotenoid Biosynthetic Pathway.



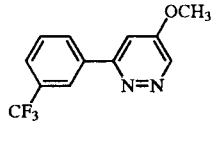
37

WGR 80: NL-0.14, BL-0.23



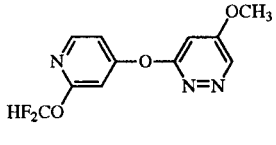
38

WGR 80: NL-0.19, BL-0.63



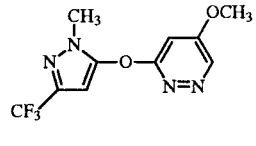
39

WGR 80: NL-1.19, BL-3.51
(Corn Selective)



40

WGR 80: NL-0.054, BL-0.17
(Corn and Wheat Selective)



41

WGR 80: NL-0.032, BL-0.042
(Corn Selective)

Figure 2. Azodiene Heterocycle Field Compounds, WGR 80 in lbs./acre

of these reactions have been published elsewhere [34-36]. The initial bleaching herbicide lead in this area was discovered *via* screening of the 3-phenylpyridazine analogs derived from these novel azodiene cyclizations.

Structure Activity Relationship of 3-Phenylpyridazines.

The azodiene synthesis provided 3-phenyl-pyridazines with alkyl and electron withdrawing substituents on the

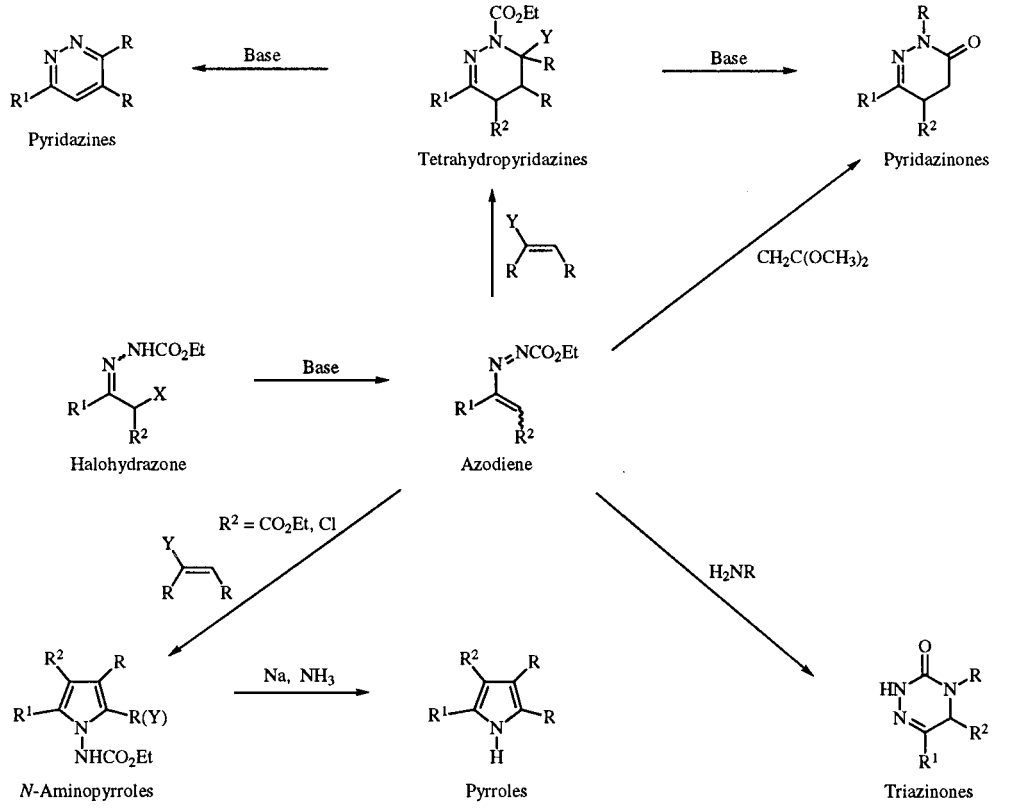


Figure 3. Reaction of Haloazodienes with Electron Rich Olefins.

The synthesis of the 3-phenylpyridazines was accomplished as outlined in Figure 4. Treatment of a dichlorohydrazone with base generates the azodiene *in-situ*. Subsequent reaction with an electron rich olefin gives good yields of the tetrahydropyridazines as separable mixtures of two diastereomers. Aromatization of the tetrahydropyridazine isomers with base leads to a variety of substituted 3-phenylpyridazines in high yield [34-36]. This reaction is compatible with a number of functional groups on the electron rich olefin and azodiene. The pyridazine derivatives were screened for herbicidal activity and were found to exhibit the bleaching symptomology.

pyridazine ring. Herbicidal activity is shown in Table 5. It was necessary to have the *meta*-trifluoromethyl substituent on the phenyl ring, as is the case with many phytoene desaturase inhibitors [22]. Other substitution patterns or differing substituents on this ring lowered the activity [26]. Substitution at the four-position [26] or six-position of the pyridazine also lowered the activity. Interesting activity in this series was obtained with a 5-methyl substituent on the pyridazine ring (compound **42** was described previously, [37]), which warranted further study.

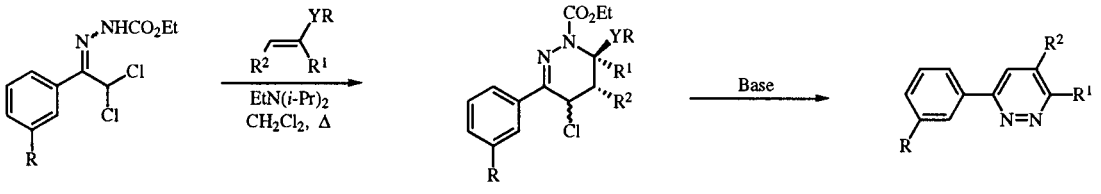
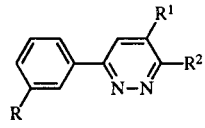


Figure 4. Synthesis of Substituted 3-Phenylpyridazines *via* Azodiene Cyclizations.

Table 5

Herbicidal Activity of 3-Phenylpyridazines



Compound	R	R^1	R^2	Primary PE	Primary POE	Secondary-PPI [a] NL	Secondary-PPI [a] BL
42	*m*-CF_3	Me	H	98, 92	62, 82	0.48	0.87
43	*m*-CF_3	Et	H	94, 82	68, 80	3.2	4.6
44	*m*-CF_3	*i*-Pr	H	68, 50	20, 6	4.9	8.1
45	*m*-CF_3	CF_3	H	64, 46	8, 10	5.6	14
46	*m*-CF_3	H	H	84, 62	16, 36	3.1	5.7
47	*m*-CF_3	H	Me	52, 42	22, 44	19	99
48	*m*-CF_3	Me	Et	46, 42	62, 88	8	10
49	H	Me	H	56, 36	10, 28	12	13
50	*m*-CF_3	H	*n*-Bu	12, 4	10, 8		
51	*m*-CF_3	*n*-Pr	Me	4, 2	20, 8		
52	*m*-CF_3	CO_2H	H	0, 0	0, 0		

[a] Primary data is percent inhibition at 10 lbs./acre pre-emergent (PE) and post-emergent (POE) for narrow-leaf (NL), broad-leaf (BL) weeds. Secondary data is WGR 80 in lbs./acre, pre-plant incorporated (PPI).

We sought to improve on the activity that was obtained in the initial 3-phenylpyridazine series through further modification of the 5-position of the pyridazine. This was accomplished by functional group transformation of the pyridazinecarboxylic acid **52** (Figure 5). Curtius rearrangement of the acid to the amine followed by chlorination *via* the Sandmeyer reaction gave chloropyridazine **54**.

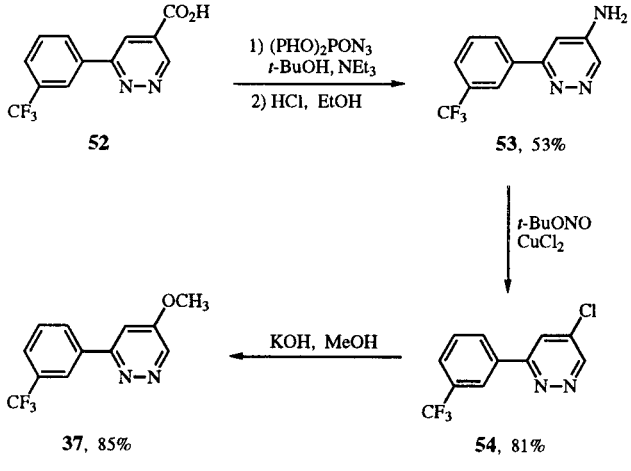
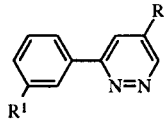


Figure 5. Synthesis of 3-(3-Trifluoromethy)phenyl-5-methoxypyridazine.

This intermediate was found to react with a variety of nucleophiles giving the analogs shown in Table 6. Treatment of **54** with potassium hydroxide in methanol gave compound **37**, which was the most active pyridazine in the 3-phenyl series. A variety of nitrogen, sulfur, and oxygen containing nucleophiles with varying substitution were incorporated at the 5-position of the pyridazine which lowered the bleaching herbicidal activity relative to the 5-methoxy substitution. Therefore, we chose the 5-methoxy substituent as the optimal pyridazine substitution for our subsequent activity and selectivity studies.

Table 6

Herbicidal Activity of 3-Phenylpyridazines



Compound	R^1	R	Primary PE	Primary POE	Secondary-PPI [a] NL	Secondary-PPI [a] BL
37	*m*-CF_3	OCH_3	98, 96	44, 42	0.14	0.23
55	*m*-CF_3	OEt	80, 64	18, 30	0.73	4.1
56	*m*-CF_3	SMe	88, 60	30, 26	1.8	5.0
57	*m*-CF_3	Cl	92, 66	8, 20	3.6	7.8
58	H	OCH_3	60, 64	44, 72	4.9	4.5
59	*m*-CF_3	$N(CH_3)_2$	54, 18	12, 24	5.3	5.4
60	*m*-CF_3	OCH_2CHCH_2	54, 34	16, 34	5.9	9.5
61	*m*-CF_3	OCH_2CCH	42, 12	42, 54	7.3	8.9
62	*m*-CF_3	$NHCH_3$	50, 26	12, 6	7.9	7.3
63	*m*-CF_3	O-*n*-Pr	44, 4	0, 4	9.1	70
64	*m*-CF_3	O-*i*-Pr	32, 8	26, 26	13	16
65	*m*-CF_3	$ONMe_2$	34, 26	24, 38	26	40
66	*m*-CF_3	OH	18, 0	36, 4	32	99
67	*m*-CF_3	NH_2	6, 0	0, 2		

[a] Primary data is percent inhibition at 10 lbs./acre for narrow-leaf (NL), broad-leaf (BL) weeds. Secondary data is WGR 80 in lbs./acre.

One additional compound that is noteworthy from the 3-phenylpyridazine series is the 5-difluoromethoxy substituted pyridazine **39** (Figure 6). This compound was somewhat less active than the 5-methoxy analog **37**, but was corn selective and served as a design template for future compounds where further selectivity enhancements with retention of activity were achieved (see selectivity discussion below).

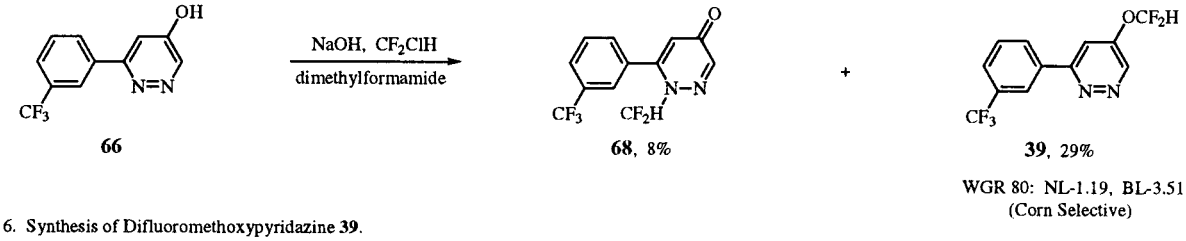


Figure 6. Synthesis of Difluoromethoxypyridazine **39**.

A-Link-B Model.

Our studies of the substitution on the pyridazine ring resulted in the optimal group being chosen as the 5-methoxy substituent (compound **37**) on the pyridazine ring (B-ring) for good activity and the 5-difluoromethoxy group (compound **39**) for selectivity. We next turned our attention toward improving the activity and selectivity based on an A-Link-B model, Figure 7. We sought to vary the ring containing the *m*-trifluoromethyl group as well as the linking group between the two rings. This approach required the development of a different route for the construction of the two ring system since the azodiene chemistry described in Figure 4 was not amenable to this strategy. We developed a large scale synthesis of 3-chloro-5-methoxypyridazine **69** [38] which served as the B-ring source for coupling with a variety aryl and heteroaryl groups (Figure 7).

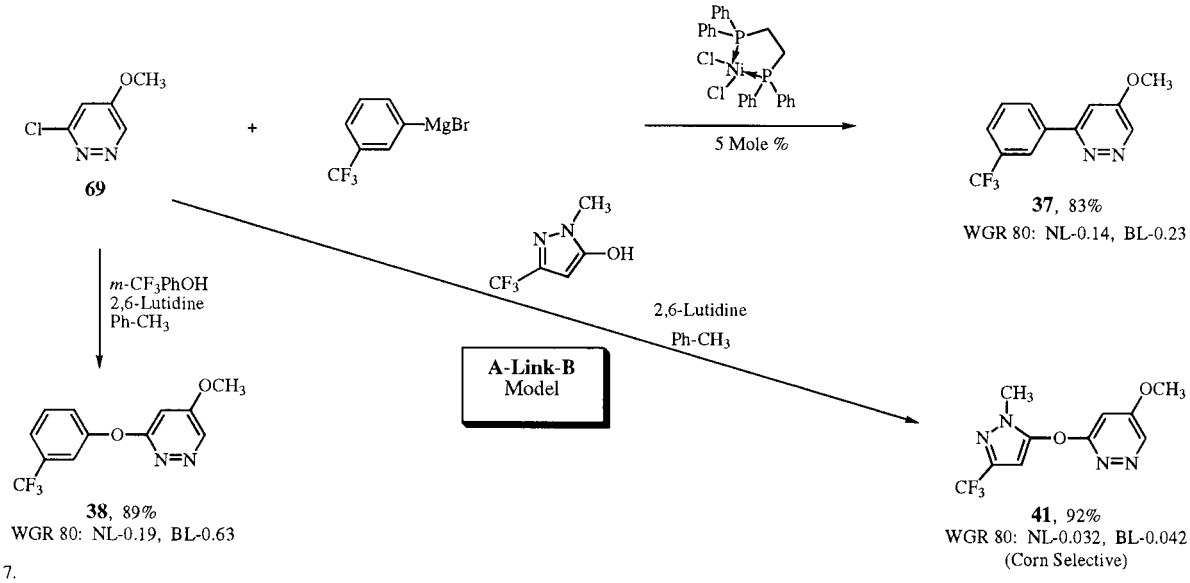


Figure 7.

Chloropyridazine **69** was found to undergo a nickel catalyzed cross coupling reaction with a Grignard reagent to give the previously prepared 3-phenylpyridazine **37** in 83% yield. Reaction of **69** with *m*-trifluoromethylphenol and base resulted in the formation of oxygen linked compound **38** in 89% yield. Greenhouse data suggested that this analog retained the activity exhibited by the directly linked pyridazine **37** while gaining some selectivity in corn and small grains. A number of arylphenols were coupled to pyridazine **69** with no improvement in activity or selectivity [27].

Large gains in activity were obtained when a pyrazolyloxypyridazine **41** [28] was prepared utilizing the same coupling chemistry used for the phenols. This compound proved to be one of the most active bleaching agents that inhibit phytoene desaturase [25] developed to date and underwent field trails in corn in the US and small grains in Europe. Compound **41** exhibited selectivity in these crops mainly through placement (soil mobility was limited under normal rainfall) in the top 1 inch of the soil surface.

Due to the superior activity exhibited by **41** and in order to study the structure activity relationship around the A-ring we developed a synthesis of fluorinated pyrazoles that relied on the chemistry shown in Figure 8 [28]. Here the fluorinated group on the pyrazole was varied through conversion of the acid fluoride to a fluorinated acetoacetate. Cyclization with methylhydrazine gave the various

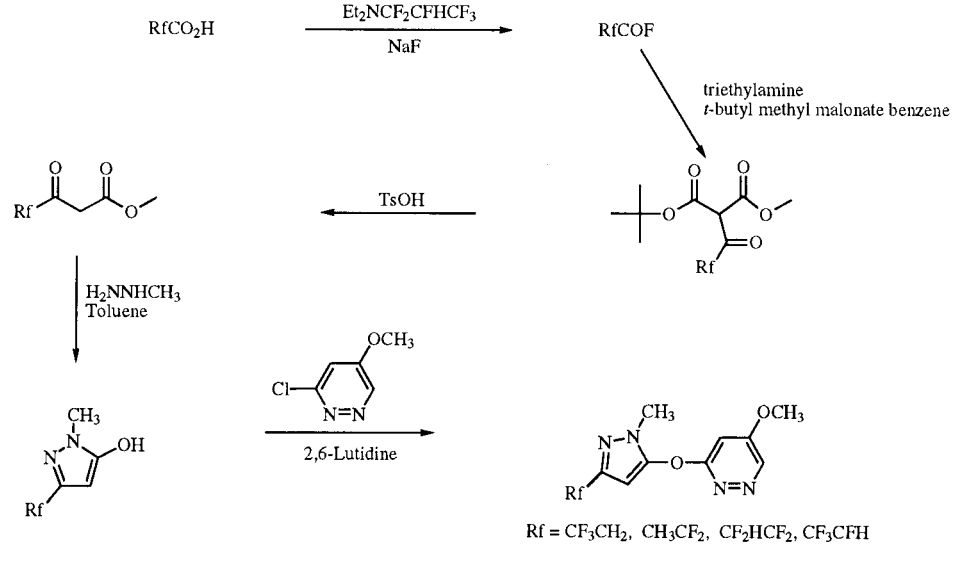
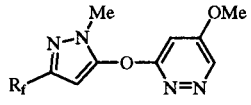


Figure 8. Synthesis of Fluorinated Pyrazoles.

substituted pyrazoles which were coupled with 3-chloro-5-methoxypyridazine to give the analogs shown in Table 7. Some of these analogs were prepared *via* functional group transformations on the pyrazole moiety [28].

Table 7

Herbicidal Activity of Pyrazolyloxypyridazines



Compound	R_f	NWW-GR80 [a]
69	CF_2CF_3	0.015
70	CH_3CF_2	0.029
40	CF_3	0.032
71	HCF_2CF_2	0.130
72	$CH_2=C(CF_3)$	0.150
73	CF_3CH_2	0.170
74	$CF_3CH(OCH_3)$	0.540
75	$CF_3CH(OH)$	0.730
76	$CF_2=CH$	0.920
77	$CF_2=CF$	1.100
78	$CH_2=C(CH_3)$	1.300
79	$CF_3CF_2C(OCH_2CH_2O)$	1.500
80	$CF_3(CF_2)_5CO$	1.800
81	CF_3CO	2.200
82	HCF_2O	2.300

[a] Narrow-leaf weed warm season GR80 in lbs./acre.

Structure Activity Relationship Studies of Pyrazolyloxypyridazines.

A variety of substituents were incorporated into the pyrazolyloxypyridazines as shown in Table 7. Structure activity relationship studies of this series is summarized in Figure 9. The best activity was obtained with small fluorinated groups of two carbon atoms or less in the three position of the pyrazole. Larger functionality at the 3-position of the pyrazole lowered the activity. The pentafluoroethyl functionality at this position was about two times more active than the trifluoromethyl functionality. Larger substitution than ethyl on the nitrogen of the pyrazole ring lowered the activity. Placing the methyl group on the other pyrazole nitrogen as well as substitution in the four position lowered the activity. Changing the linking atoms to anything except difluoromethyl or oxygen lowered the activity.

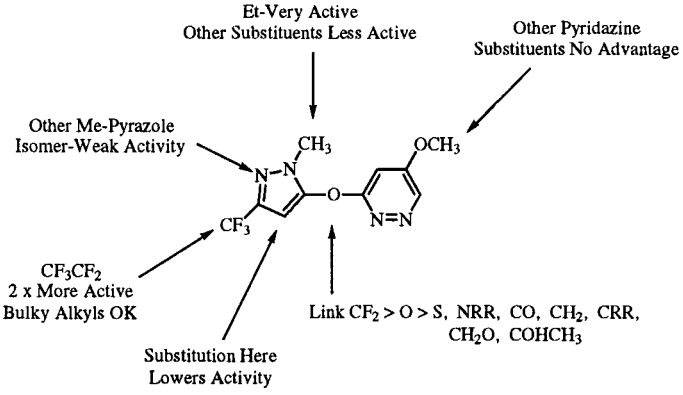


Figure 9. Structure Activity Relationship Studies of Pyrazolyloxypyridazines.

Structure Activity Relationship Studies of Alternate Heterocycles.

Using the chemistry described above (Figure 7) a variety of heterocycles were coupled with the 3-chloro-5-methoxypyridazine **69** (Figure 10). Pyridine and triazole heterocycles substituted with small fluorinated groups were all found to be quite active as compared to the pyrazole substitution. The pyridine moieties were also found to impart some metabolic selectivity that was superior to the other analogs synthesized and tested so far. The pyridine A-rings were advanced for further synthesis and testing due to their enhanced selectivity profiles and are discussed in the next section.

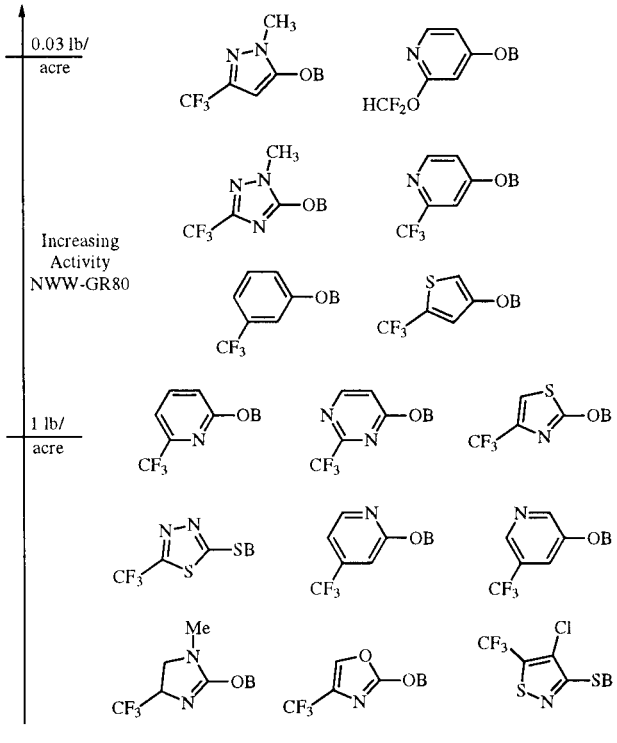


Figure 10. Structure Activity Relationship Studies of Alternate Heterocycles.

Synthesis and Structure Selectivity Studies.

Building in Metabolic Selectivity with Retention of Activity.

Large gains in efficacy were obtained in the pyridazine area of chemistry *via* the development of new compounds using the A-Link-B model described above. The activity of the directly linked 3-phenylpyridazine **37** was improved upon by introducing an oxygen linking atom between the two rings to give 3-phenoxypyridazine **38** followed by optimization of the A-ring heterocycle to give the pyrazolyloxypyridazine **41**. These compounds performed well in greenhouse and field testing, however, much of their selectivity was derived from what is termed placement selectivity and not from metabolic selectivity. Studies indicated that most of active ingredient was found in the top one inch of soil in greenhouse and field situations after normal rainfall amounts. Most weeds germinate in this zone containing the herbicide while the crop in question is planted below this 1 inch level. Greenhouse and field crop injury was noted when compounds **37**, **38**, and **41** migrated into the zone of germination of the crop (2-4 inches) due to heavy rainfall conditions or soil surface disturbance.

Metabolic selectivity is defined as the ability of the crop species to metabolize the herbicidal compound in question to an inactive form *via* a pathway that is not present in the weed species to be controlled. One such metabolic pathway is conjugation with glutathione catalyzed by glutathione S-transferaces. Corn and to a lesser extent small grains have high levels of glutathione. We sought to utilize the glutathione metabolic pathway to our advantage in the pyridazine area to design a corn and/or wheat selective compound while maintaining the activity against important weed species.

We knew that compound **39** had exhibited (Figure 11) a high level of selectivity in corn from our previous studies with a selectivity factor of 7.12 (selectivity factor = Corn GR20/NWW GR80, larger numbers equal better selectivity) and a somewhat moderate narrow-leaf weed warm season GR80 (NWW GR80) of 0.33 lbs./acre. In an effort to understand this selectivity, compound **39** was incubated with glutathione in the presence and absence of glutathione S-transferaces. Both experiments led to conjugation of **39** with glutathione through replacement of the labile OCF_2H group with the sulfhydryl group of glutathione (B. Molin, unpublished results). We also knew that compound **82** exhibited high levels of activity (NWW GR80 0.037 lbs./acre) with poor selectivity in corn (selectivity factor = 0.84). We theorized that replacing the OCF_2H group on the pyridazine with the optimal 5-methoxy group and moving the OCF_2H group to the labile position alpha to the pyridine nitrogen would give an ana-

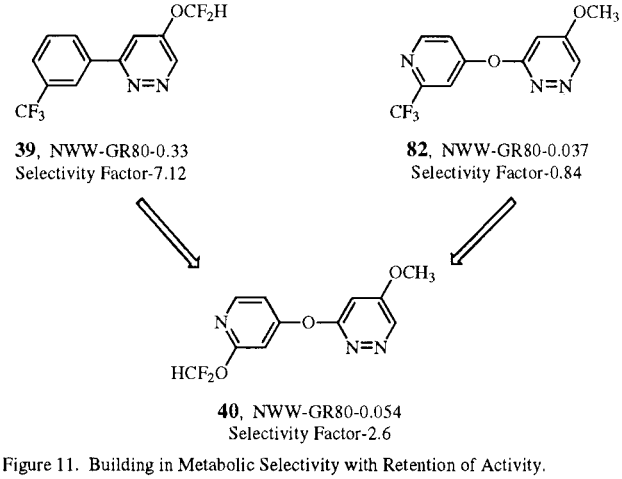


Figure 11. Building in Metabolic Selectivity with Retention of Activity.

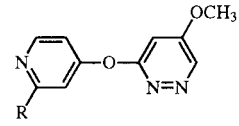
log with good selectivity and activity profiles. Synthesis (Figure 12) and testing of compound **40** proved that this was indeed the case. Compound **40** was not only highly active (NWW GR80 0.054 lbs./acre), but also selective in corn (selectivity factor of 2.6).

Due to the activity and selectivity profiles exhibited by compound **40** we developed a new synthesis of the pyridyloxypyridazines [29] as outlined in Figure 12 so that further structure activity relationship and structure selectivity studies could be defined. The synthesis relied on the conversion of a protected pyridone to a fluorinated alkoxy group or displacement of an *ortho*-chloropyridine with a nucleophile.

Activity data for selected pyridyloxypyridazines is shown in Table 8. A number of small fluorinated alkoxy groups were tolerated *ortho* to the pyridine nitrogen. Compounds **84-87** were as active as compound **40** with similar selectivity profiles. None of the compounds listed in Table 8 was superior to compound **40** in field test in corn and small grains. This series was used however to demonstrate that the soil mobility could be adjusted based on the lipophilicity of the fluorinated side chain (longer fluorinated side chains imparted less soil mobility).

Table 8

Structure Activity Relationships of Pyridyloxypyridazines



Compound	R	NWW-GR80 [a]
40	HCF_2O	0.054
84	CF_3CH_2O	0.032
85	$CF_3(CH_3)CHO$	0.030
86	HCF_2S	0.040
87	$HCF_2CF_2CH_2O$	0.030

[a] Narrow-leaf weed warm season GR80 in lbs./acre.

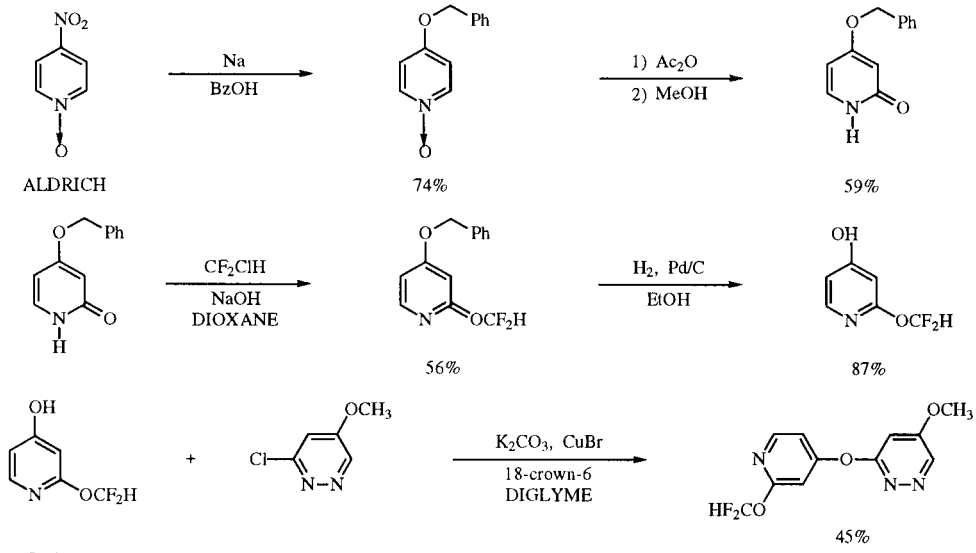


Figure 12. Synthesis of Pyridyloxypyridazines.

Summary of Structure Activity Relationship and Structure Selectivity Studies.

A summary of the structure activity and structure selectivity relationships in the pyridazine area are shown in Figure 13. The initial lead (compound **37**) in this area was discovered as a result of the development of the novel cyclization of an azodiene with an electron rich olefin giving a 3-phenylpyridazine. Functional group manipulation resulted in the 5-methoxy group being chosen as the optimal group on the pyridazine ring. Compound **37** was not selective on corn (selectivity factor 1.92). Introduction of an oxygen link in between the two rings (compound **38**) maintained the bleaching herbicidal activity while

increasing the selectivity in corn (selectivity factor 4.38). Functionalization at the 5-position of the pyridazine ring with an OCF_2H group (compound **39**) imparted high levels of corn selectivity (selectivity factor 7.12) due to metabolic displacement and inactivation with glutathione. Utilizing a A-Link-B strategy, the optimal heterocyclic A-ring was chosen as the pyrazole in compound **41**. This analog is one of the most active bleaching agents that inhibits phytoene desaturase that has been developed to date. Combining the OCF_2H selectivity element with the pyridine A-ring resulted in compound **40** which proved to be one of the most highly active and corn selective analogs in this series.

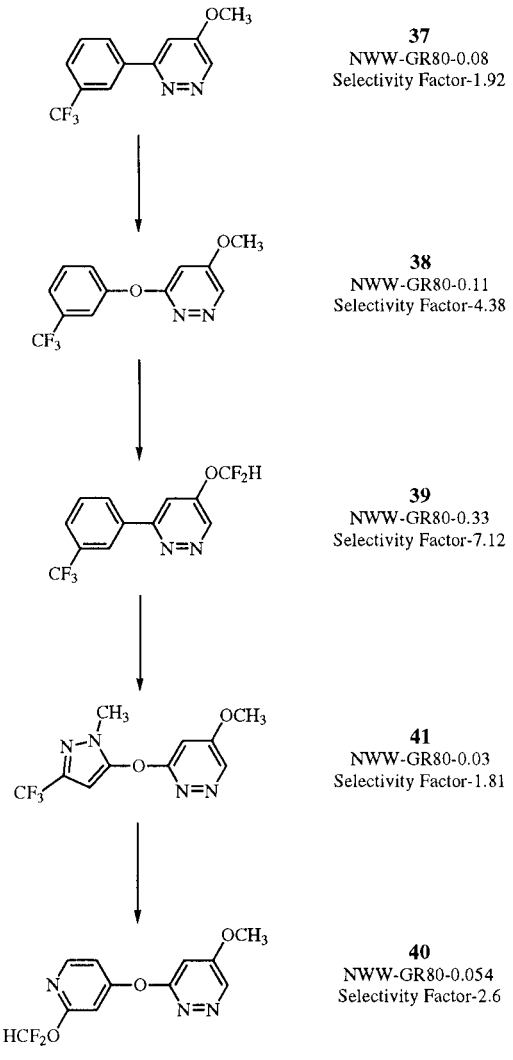


Figure 13. Summary of Structure Activity Relationship and Structure Selectivity Studies.

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