Chapter 9

Phenyl-Substituted Five-Membered-Ring Heterocycles as Bleaching Herbicides

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Since its discovery in 1974 (*1*)the structure of fluorochloridone (**1**) has been extensively examined in the search for more active and selective bleaching herbicides. This chapter provides an overview of the work which determined the features of **1** critical for activity and structural modifications that increased its overall activity nearly ten-fold. In addition, modification of the 5-membered ring nucleus to include variously substituted imidazolidones, oxazolidines, thiazolidines, and pyrrolidines which resulted in several new series of very active bleaching herbicides is also presented.

The discovery of fluorochloridone (**1** Figure 1), the active ingredient in Racer herbicide, was made possible by an unexpected occurrence during the thermal stability testing of herbicide antidote R-25788. When heated in a sealed iron vessel at 50° for several months the sample of R-25788 slowly underwent an unprecedented (at the time) iron-catalyzed chlorine transfer cyclization reaction to form pyrrolidone R-37878. Unlike its precursor, which is herbicidally inert, R-37878 proved to be an effective pre-emergence grass herbicide which produced symptoms similar to those exhibited by the chloroacetanilides. During a subsequent synthesis program to prepare analogs of R-37878 the symptomology underwent a radical change when the allyl group on nitrogen was replaced with a phenyl ring: from chloroacetanilide-like to the strong bleaching characteristic of a carotenoid biosynthesis inhibitor. The placement of a CF_3 group at the 3-position of the phenyl ring to form **1**, carried out very soon thereafter, resulted in a substantial increase in the level of bleaching activity to where broad spectrum pre-emergence weed control could be achieved in the field at 250-300 g/ha. *In vitro* testing of **1** showed it to indeed be a strong inhibitor of phytoene desaturase, an enzyme in the carotenoid biosynthesis pathway (*2*).

Pyrrolidones

Possessed with high levels of activity and marginal crop selectivity **1** became the focus of an ambitious effort to elucidate its structure/activity relationships (SAR) and to discover more active and/selective molecules. Since **1** is formed as a 3:1 mixture of *trans* and *cis* isomers the initial work involved chromatographic separation of the two. The more abundant *trans* isomer, whose stereochemistry was

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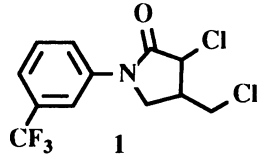
proved by X-ray crystallography (*3*), was found to be approximately three-fold more active than the *cis* isomer on whole plants.



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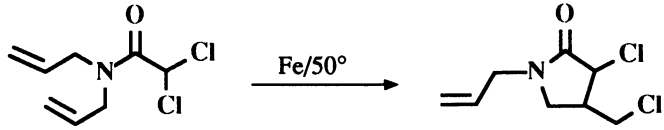
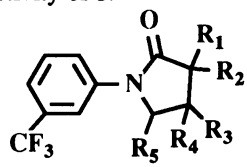


R-25788 R37878

Figure 1

The next phase involved an exhaustive exploration of phenyl ring substitution in which several hundred analogs with numerous functional groups placed at various positions were prepared. In general this showed that the 2-,4- and 6-positions of the aromatic ring could not be substituted with anything larger than a fluorine atom and although 3,5-disubstitution produced active molecules these were always less active than those with a single substituent at the 3-position. When none of the phenyl ring variants proved to be more active than **1** the synthetic effort was directed toward modifying the more challenging pyrrolidone ring.

The first variations in the pyrrolidone ring (Figure 2), achieved primarily using the copper catalyzed cyclization conditions developed by Broadhurst (*4*), demonstrated the importance of this portion of the molecule for overall activity. For example, removal of the chlorine atom at the 3-position of the pyrrolidone ring with zinc/copper couple (**2**) resulted in an approximately four-fold decrease in *in vivo* activity. The addition of a second chlorine atom or a methyl group to this position (**3** and **4**) gave similar results. Activity was lost altogether when a methyl group was added to the 4-position (**5**) and when a second chlorine was added to the chloromethyl group (**6**). If the chloromethyl group was replaced by hydrogen (**7**) all bleaching activity was also lost. The 5-position was found to tolerate no substitution at all as evidenced by the complete inactivity of **8**.



2 $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = CH_2Cl$

3 $R_1 = R_2 = Cl$, $R_3 = R_5 = H$, $R_4 = CH_2Cl$

4 $R_1 = Cl$, $R_2 = CH_3$, $R_3 = R_5 = H$, $R_4 = CH_2Cl$

5 $R_1 = Cl$, $R_2 = R_5 = H$, $R_3 = CH_3$, $R_4 = CH_2Cl$

6 $R_1 = CH$, $R_2 = R_3 = R_5 = H$, $R_4 = CHCl_2$

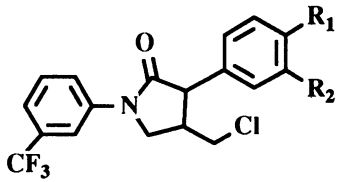
7 $R_1 = Cl$, $R_2 = R_3 = R_4 = R_5 = H$

8 $R_1 = Cl$, $R_2 = R_3 = H$, $R_4 = CH_2Cl$, $R_5 = CH_3$

Figure 2

The above observations led to the hypotheses that 1), optimum activity might depend on the presence of nucleophilic species in or near the receptor which displace one or both chlorines to covalently bind the herbicide to the protein or 2), instead of functioning as a site for covalent bond formation the chloromethyl group might just be of the proper size and lipophilicity to fit into a cleft in the protein and thus mechanically anchor the herbicide to the receptor. In the case of the chloromethyl group the available data could be used to support either nucleophilic substitution or mechanical interaction arguments. For example the 4-methyl group of **5** adds additional steric bulk which could interfere with a mechanical fit but it also makes the 4-position neopentyl, which would greatly retard nucleophilic substitution at the adjacent position. Similarly, the extra chlorine in **6** both changes the steric environment and effectively eliminates the possibility of nucleophilic substitution.

To validate or refute these ideas two key analogs were prepared in which the chlorines were replaced by groups not susceptible to displacement (Figure 3). First, the chlorine at the 3-position was replaced by a phenyl ring to give a molecule (**9**) that was essentially as active on whole plants as 1. A study of ring substitution on the 3-phenyl ring produced activity equivalent to fluorochloridone when the 3- and/or 4-positions were fluorinated (**10**). Thus *in vivo* displacement of the 3-chlorine is not required for herbicidal activity.



9 $R_1 = R_2 = H$

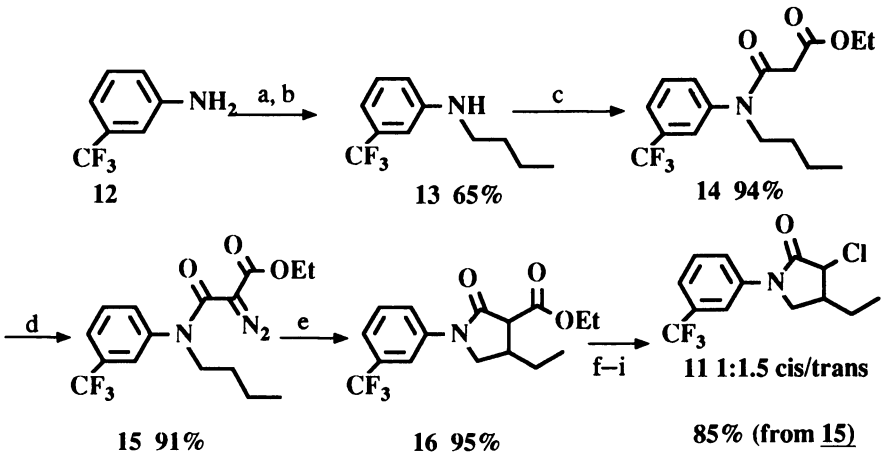
10 R_1, R_2 = 3-F, 4-H; 3-H, 4-F; 3,4-di-F

Figure 3

The possible importance of *in vivo* nucleophilic substitution at the chloromethyl group was more difficult to evaluate since the required 4-ethyl analog, **11**, could not be obtained from intermediates prepared using our standard chlorine transfer cyclization procedures. Instead m-aminobenzotrifluoride (MABTF, **12**) was butylated (**13**) and then acylated with ethyl malonyl chloride to give **14**, which was then converted to diazomalonamide **15** using p-toluene sulfonyl azide (*5*). Rhodium acetate-catalyzed decomposition (*6*) of **15** formed pyrrolidone intermediate **16** which was then converted to the desired **11** by the steps shown in Figure 4.

It was expected that if nucleophilic substitution at the chloromethyl group was important for binding at the receptor site **11** should be substantially less active than **1**. If, on the other hand, the chloromethyl group aids binding by purely electrostatic and/or mechanical means **11** should be as active as **1**. In reality **11** is approximately 2.5 times more active and completely non-selective, strongly suggesting that the chloromethyl group provides a site for metabolism and that its contribution to substrate binding is principally electrostatic in nature.

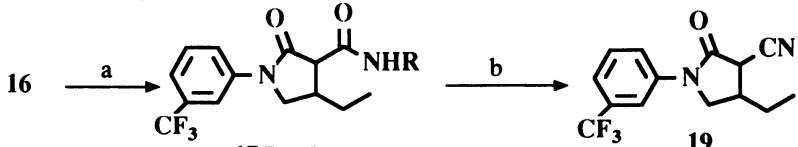
With this new route for preparing 4-ethylpyrrolidones it became possible to prepare compounds with substituents at the 3-position that were not accessible through the chlorine transfer cyclization. For example, evidence had suggested that increasing the electron withdrawing power of the 3-substituent would increase the



a) butyraldehyde/$TiCl_4$/TEA/PhH/Et_2O/0-3°; b) $NaBH_4$/EtOH (65%); c) ethyl malonyl chloride/PhH/0-5° (94%); d) p-TsN_3/TEA/CH_3CN (91%; e) $Rh_2(OAc)_4$/PhH/ reflux (95%); f) SO_2Cl_2/CH_2Cl_2; g) NaOH/MeOH; h) H_3O^+; i) 160° (85% from **15**)

Figure 4

activity of **1** and a number of attempts were made to introduce a cyano group at this position by direct substitution methods. However, all attempts to combine cyanide ion with **1** produced only complex mixtures of unidentified products. This problem was circumvented by using the simple route shown in Figure 5 to convert **16** to cyanopyrrolidone analog **19**. Unexpectedly, **19** was found to be nearly inactive at 4kg/ha while the amide precursor **17** proved to be very active. This was surprising in light of the fact that neither ester **16** nor the corresponding acid exhibit any activity at this rate. A number of analogs of **17** were then prepared which resulted in a diverse array of highly active secondary amides (*7*). For example **18**, one of the simplest, provides non-selective pre-emergence weed control in the field at a rate of approximately 30g/ha.

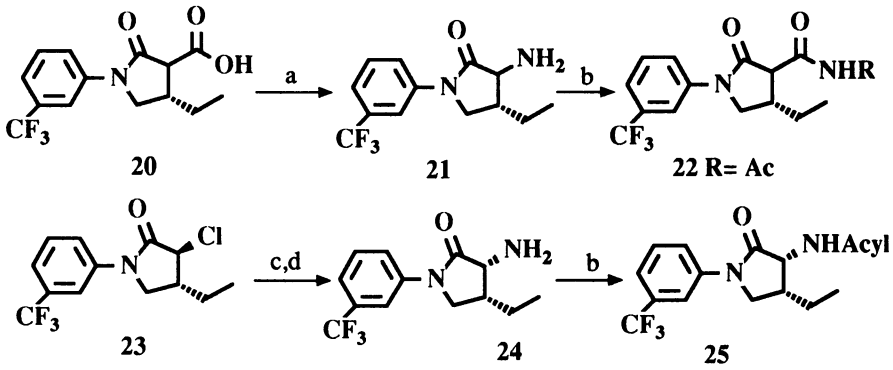


17 R = H
18 R = CH_3

a) for **16**: NH_3/MeOH (100%); for **17**: CH_3NH_2/MeOH (100%); b) P_2O_5/EtOAc/reflux (73%)

Figure 5

Another series of active pyrrolidones resulted from the availability of substantial quantities of **20** and a desire to "reverse" the amide group of **18**. Curtius rearrangement of *trans* **20** was smoothly accomplished by treatment with triphenylphosphoryl azide which gave *trans* **21** (Figure 6). The acylation of **21** with acetyl chloride afforded the "reversed" amide **22** which proved to be as active as **18**.



a) Ph_3PON_3/TEA/reflux (100%); b) acylation (100%); c) NaN_3/DMF/50° (69%); d) H_2/Pd (100%)

Figure 6

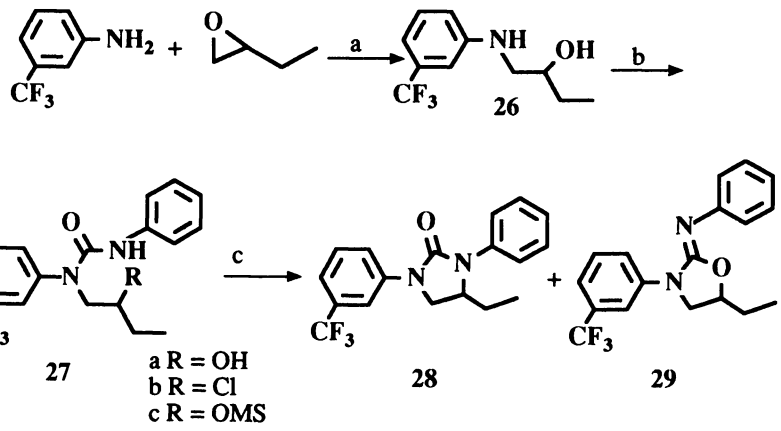
Further acylation reactions with acyl and sulfonyl halides, isocyanates, and isothiocyanates provided a number of active herbicides whose efficacy decreased with increasing size of the "acyl" group. The corresponding *cis*-isomers could be prepared by treating *trans* **11** (**23**) with sodium azide followed by reduction and acylation. Without exception these compounds were found to be three to four-fold less active than their *trans*-counterparts.

Imidazolidones and 2-Phenyliminothia(oxa)zolidines

With the knowledge that activity in the pyrrolidone series can vary greatly depending on the electronic nature of the 3-substituent it was decided to introduce an unshared pair of electrons at this position by replacing the carbon atom with a nitrogen. This was accomplished by combining anilinoalcohol **26** with phenylisocyanate and converting the hydroxyl group of the resulting urea (**27**) to an efficient leaving group by reaction with either $SOCl_2$ or mesyl chloride (Figure 7). Treatment of either **27b** or **c** with a strong, non-nucleophilic base to effect ring closure gave low yields of the desired thermodynamic product, imidazolidone **28**, and varying amounts of the kinetic product, 2-aryliminooxazolidine **29** (*8*). The two (**28** and **29**) were laboriously separated by column chromatography only to find that both were nearly inactive at 4kg/ha. Similar disappointing results were observed with imidazolidones and oxazolidines prepared from a variety of phenylisocyanates with one exception: the cyclization of the urea prepared with 4-cyanophenylisocyanate produced a poor yield of a single compound that was extremely active at 4kg/ha.

The mass spectrum of this material, which clearly showed the presence of a single sulfur atom, and irregularities in the nmr spectrum ruled out the expected structure (**30**). The identity of this new material was fixed when it was shown that the new bottle of phenylisocyanate, labeled as such by the supplier, really contained the isothiocyanate. This meant that **31**, which fit the spectral data, was the correct structure of the new active compound since sulfur would be expected to overwhelmingly dominate the ring closure reaction.

Thiazolidine **31** provided excellent pre-emergence weed control at 500g/ha and offered the potential for a new series of bleaching herbicides if an efficient synthesis of this ring system could be developed. One report in the early literature (*9*) described



a) neat/reflux; b) ArNCO/MeCN; c) $SOCl_2$ or MsCl/py then t-buOK

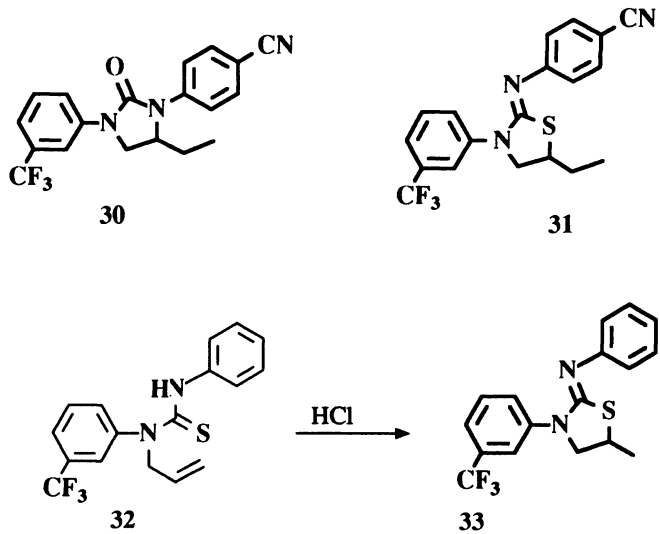
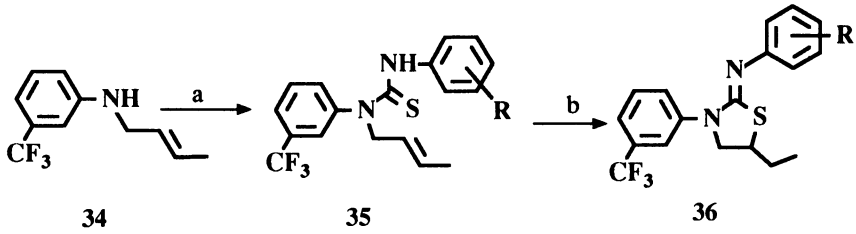


Figure 7

the preparation of a phenyliminothiazolidine of this type from an allylthiourea by refluxing in concentrated HCl (32 → 33).

We found these conditions to be incompatible with sensitive functional groups and the reaction failed altogether when the allyl group was replaced by a crotyl residue. Therefore we developed the route shown in Figure 8 (*10*) which provided a variety of thiazolidines in good to excellent yields.



34 35 36

a) PhNCS/MeCN (45-95%); b) CF_3SO_3H/MeCN/RT (65-95%)

Figure 8

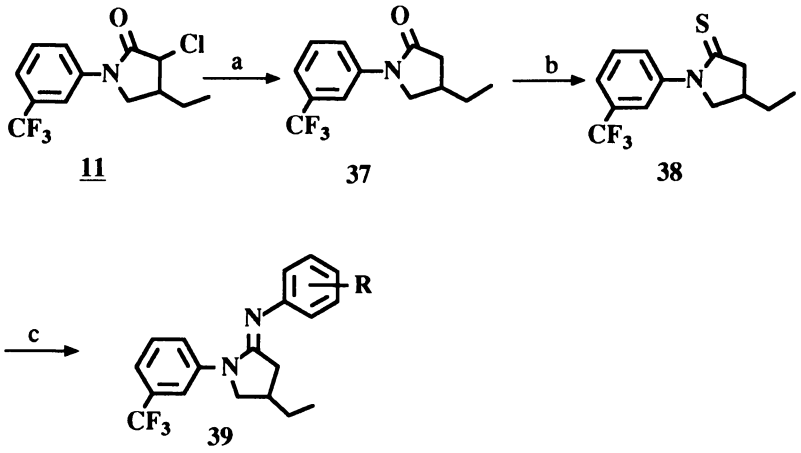
As with the pyrrolidones a 3-CF_3 group was found to be the most effective substituent on the 3-phenyl ring. A study of substitution on the iminophenyl ring showed that electron withdrawing groups at the 3- and/or 4-positions provided the best activity; compound **36** (*11*) (R=4-F) in the field controls grass and broadleaf weeds pre-emergence at 250g/ha and provides complete broadleaf control post-emergence at rates as low as 15g/ha.

2-Phenyliminopyrrolidines

The fact that sulfur, and to some extent oxygen, could occupy the position equivalent to the 3-position of the pyrrolidone ring and provide high levels of bleaching activity led us to consider reintroducing carbon at this position. The 2-phenyliminopyrrolidines that resulted were prepared from **11** as shown in Figure 9. The yields of the final products were found to depend on the the electron withdrawing capability of the substituent(s) on the aniline and the reagent used to oxidize the thiopyrrolidone. For example, using MCPBA as the oxidant to combine **38** and aniline resulted in an 85% yield of the corresponding **39** while the reaction with 4-aminobenzonitrile proceeded in only 32% yield. The remainder of the mass balance was accounted for by the conversion of **38** back to **37** by reaction of the oxidizing thione with the carboxyl group of the oxidant. It was found that when SO_2Cl_2 was substituted for MCPBA the formation of **37** was minimized and the yields of **39** averaged 95%. The pre-emergence activity of the best of these compounds (**39**,R=4-F) in the field was slightly better than that of **1** with slightly improved cereal selectivity.

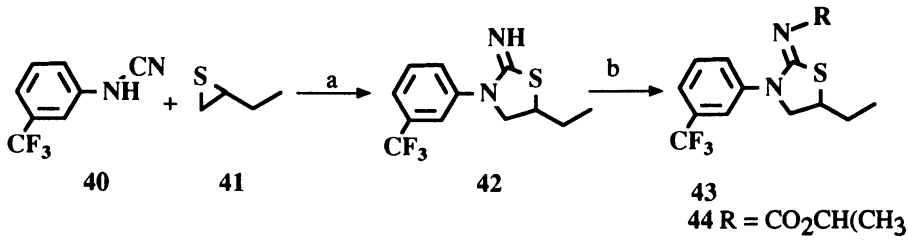
2-Acylaminothiazolidines and Pyrrolidines

Developments in another active series not discussed here pointed to the possibility that an acyl group might serve as a replacement for the phenyl ring on the imino nitrogen of the thiazolidine and pyrrolidine series. We found that the required iminothiazolidine intermediate **42** could be conveniently prepared by refluxing cyanamide **40** (*12*) and **41** in methyl ethyl ketone (MEK) in the presence of K_2CO_3 (Figure 10). Thiazolidine **42** was found to react readily with a variety of acid halides, isocyanates, isothiocyanates (*13*), and sulfonyl halides (*14*) to give a variety of herbicidally active structures (**43**). Among the most active of these **44** provides excellent post-emergence broad leaf weed control in the field at 63g/ha as well as control of many grass species.



a) Zn-Cu/MeOH/reflux (100%); b) P_2S_5/THF/reflux (75%); c) MCPBA or $SO_2Cl_2/PhNH_2/CH_2Cl_2/0°$

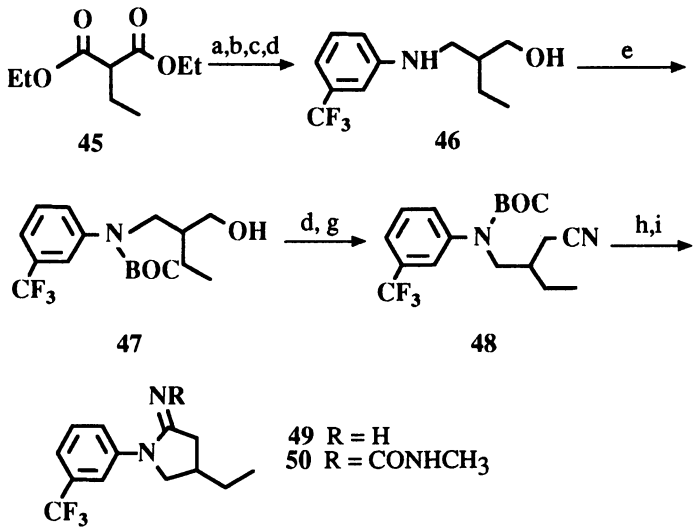
Figure 9



a) K_2CO_3/MEK/reflux (85%); b) acylation (85-100%)

Figure 10

The synthesis of 2-iminopyrrolidine intermediate **49** was accomplished in 47% overall yield using the standard reactions shown in Figure 11. As with **43** **49** was found to react with a wide variety of acylating reagents but the substitution of the sulfur atom in the ring with carbon had a deleterious effect on the overall activity. In general the acyliminopyrrolidines were very active bleaching herbicides at rates of 1-2 kg/ha but below this level activity fell off very sharply. Compound **50** was the only exception to this and maintained acceptable levels of pre-emergence weed control at 125 g/ha.

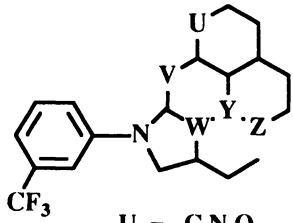


a) KOH/EtOH the HCl; b) $SOCl_2$/Ph; c) MABTF/py; d) LAH/THF (51% from **45**); e) $(Boc)_2O$ (99%); f) TsCl/py; g) KCN/DMF (93%); h) HCl/Et_2O then NaOH (100%); i) acylation (90-100%)

Figure 11

Conclusion

From the preceding discussion it is clear that a substantial number of modifications can be made to the two-ring system of **1** to increase the original level of bleaching activity. When combined these various modifications define a two-dimensional structure/ activity space (Figure 12) that we have successfully used for the design of new bleaching herbicides. In general, the most active compounds in any series always contain a CF_3 group on the 3-position of the phenyl ring and an ethyl group on the position analogous to the 4-position of the pyrrolidone ring of **1**. The chlorine on the 3-position of the pyrrolidone ring in fluorochloridone can be replaced with phenyl, substituted phenyl, alkylthio, phenylthio, phenoxy, and carboxamido groups. The carbon atom at this position can be replaced by sulfur and in some limited instances by oxygen and nitrogen. Finally, the carbonyl group of **1** can be replaced by an imino nitrogen which bears either a substituted phenyl ring or a variety of acyl groups.



U = C,N,O
V = N,O,S
W = C,S,O
X = C,N,O,S
Y = C,N,O,S
Z = C,N,O

Figure 12

Acknowledgments

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