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Studies on the synthetic development for the discovery of novel heterocyclic agrochemicals*

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Various heterocyclic compounds have significantly contributed to current commercial agrochemicals. We focused our attention on these heterocycles as screening targets to create novel bioactive compounds. Although recent progress in agrochemical research has enabled us to discover drugs directly, we selected a chemical approach to *N*- and *N*,*S*-heterocyclic compounds in an expectation of new chemical classes with biological activity. In consequence, this method led to the generation of four heterocycles which had either herbicidal or fungicidal activity. These heterocycles were extended to optimized compounds, resulting in the discovery of three herbicides (2,4-diphenylpyrimidine, 2-acylimino-1,3-thiazoline and 5-trifluoromethylpyridazinone) and one fungicide (2-pyridylpyrimidine). © Pesticide Science Society of Japan

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Introduction

There are a number of approaches to the discovery of agrochemicals. Those usually discussed include random screening, patent following, using natural products as the basis for invention, and biochemically oriented rational design. In spite of recent progress in drug discovery based on these approaches, we applied a chemical approach to identify novel *N*- and *N*,*S*-heterocyclic compounds with interesting biological activities.

Until now, this method has served as a rich source to discover a number of heterocyles. In the process of synthesizing *N*-heterocycles using such heterocumlenes as acyl isothiocyanates, we found weak herbicidal activity for 2,4-diphenyl-1,3,5-triazines and 2-acylimino-5-methylene-1,3-thiazolidines, respectively. These new herbicides showed bleaching symptoms at *ca*. 8.0 kg/ha in both cases. On the basis of their structure–activity relationships, these heterocycles were extended to optimized compounds, producing novel bleaching herbicides, 2,4-diphenylpyrimidine and 2-acylimino-1,3-thiazoline.

Furthermore, our chemical approach was directed to the structural modification of the two known heterocyclic herbicides, imadapyr and flupropacil, as a template. From the former, we accidentally found triazoylpyridines with fungicidal activity. From the latter, on the other hand, phenylpyridadinones were selected as the initial lead. Successively, structural optimization of these heterocycles led to a novel fungicide, 2-pyridylpyrimidine and a peroxidizing herbicide, 2-phenyl-5-trifluoromethylpridazinone. In this article, a summary of the discovery, synthesis and structure–activity relationships of these heterocycles will be presented.

1. Discovery of bleaching herbicides

1.1. Diphenylprimidines

While working on the synthetic development of various heterocycles using heterocumulenes such as acyl isothiocyanates, we happened to identify weak herbicidal activity of 2-(2-chlorophenyl)-5-methoxy-6-phenyl-1,3,5-triazine which showed bleaching symptoms. Considering the structural similarity and the characteristic symptoms of known bleaching herbicides, this finding prompted the preparation of additional analogs.

* See Part II for the full Japanese article.

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Following further optimization of herbicidal activity, we soon became aware of a great increase in activity when going from the initial lead, 1,3,5-triazine nucleus, to the pyrimidine ring. To clarify the structure–activity relationships of substituted 2,4-diphenylpyrimidines, we required access to highly substituted pyrimidin-4(3*H*)-ones, which were key intermediates to prepare the desired compounds. Consequently, we found new transformation reactions of labile heterocycles, oxazinones and azetidinones, into 2,4-diphenylpyrimidin-4(3*H*)-ones. These heterocycles were easily converted into the corresponding 5-chloro derivatives, followed by treatment with various nucleophiles to give 5-and/or 6-substituted and 5,6-disubstituted 2,4-diphenylpyrimidines.

An alternative route to synthesize the most active 2,4-diphenyl-5-methoxy-pyrimidines was also examined. Toward solving this problem, 2,4-diphenyl-5-methylsulfonyl-pyrimidines prepared according to the known method were selected as key intermediates. Nucleophilic displacement of 5-methylsulfonylpyrimidines with sodium methoxide afforded the corresponding 5-methoxy derivatives. By using these new processes, a variety of biologically active 2,4-diphenylpyrimidines were produced for testing. Thus, various structural modifications based on the 2,4-diphenyprimidines resulted in the creation of 2-(4-fluorophenyl)-5-methoxy-4(3-trifluorophenyl)pyrimidine with broad spectrum weed control and cereal safety when applied postemergence.

1.2. Acyliminothiazolines

Starting with a commercially available ethoxycarbonyl isothiocyanate out of various heterocumulenes, we studied the cyclization reaction of labile thioureas formed by reaction with *N*-propargyl anilines. As a result, we found a new transformation reaction of thioureas into a novel heterocycle, 2-(*N*-ethoxycarbonylimino)-5-methylene-1,3-thiazolidine. Among the 1,3-thiazolidines prepared for the herbicidal evaluation test, 3-(3-chlorophenyl)-5-methylene-1,3-thiazolidine showed weak herbicidal activity with bleaching symptoms, which encouraged us to examine by systematic screening of a novel heterocycle as a herbicide lead for a new bleaching herbicide. Intriguingly, there was a dramatic change in activity when going from the thiazolidine ring to the thiazoline nucleus as the second lead.

At a starting point to structurally optimize the second lead, we divided the core structure into three subsections, the phenyl, the imino group, and the thiazoline nucleus. For the phenyl moiety, *meta*-substitution was preferred over *ortho* or *para*-substitution, and a trifluoromethyl group turned out to be the optimum *meta*-substituent. When we brought the imino group into focus, this position was most critical for herbicidal activity and crop selectivity, indicating that the best subsitutuent was difluoroacetyl. Concerning activity optimization at the 4- and 5-positions on the thiazoline ring, optimum activity was seen when hydrogen was at position 4 and methyl at position 5. Among the compounds examined, 2-(*N*-difluoroacetylimino)-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazoline was finally selected as a most promising candidate for precommercialization.

2. Discovery of pyridylpyrimidine fungicides

A new class of fungicides was discovered as a result of speculative chemistry in an attempt to introduce a carboxylic group into the pyridine nucleus. When triazoylpyridine was reacted with carbon dioxide in the presence of *n*-butyllithium, an unexpected reaction occurred to give *n*-butylated pyridines, one of which turned out to have interesting fungicidal activity. Having high-level activity and broad fungicidal spectrum, this product became a clue in our efforts to elucidate its structure–activity relationships and to discover more active molecules.

During the early stages of the program, a variety of substitution patterns were investigated. It soon became clear that a 2,6-disubstituted pyridine ring was required for fungicidal activity. This led us to replace the *n*-butyl group in the 6-position of the pyridine ring with a phenyl moiety, which resulted in increased activity.

Activity optimization of position 6 led to the finding that a *o*-tolyl group gave the most active compound in these series, with a broad spectrum of fungicidal activity. The next two breakthroughs occurred almost simultaneously. The first came about from replacement of the five-membered ring with the six-membered ring heterocycle at position 2 of the pyridine ring. Dramatically, increased biological activity was observed when going from the 1,2,4-triazole ring to the pyridine ring.

The second striking change in activity came from replacement of the pyrimidine ring with the pyridine moiety. Activity optimization of a substituent on the pyrimidine ring was seen for the methyl group at position 3.

On the basis of the limited structure–activity relationships found here, 4-methyl-2(6-*o*-tolylpyrdinyl)pyrimidine was finally selected as a promising candidate for precommercialization.

3. Discovery of phenylpyridazinone peroxidizing herbicides

The herbicidal properties of phenyluracils have been known since the late 1980s, when workers at Hoffman-La Roche first described 3-phenylpyrimidindiones as a promising new class of herbicide. Other groups later reported that the addition of a trifluoromethyl group at position 6 on the pyrimidindione ring increased herbicidal activity greatly. Among the compounds prepared, flupropacil was commercialized as a nonselective herbicide.

Focusing on both a unique structure and high herbicidal activity, flupropacil was chosen toward the structural optimization of the heterocyclic ring, the phenyl ring and its substituents. First, to examine the effect of the hetrocyclic ring on activity, we synthesized the 2-phenylpyrizazinones, which possess a trifluoromethyl group at position 5. This dramatic structural change provided better control of broadleaf weeds

with crop tolerance for soybean and corn. Secondly, our attention turned to optimal subsititution on the phenyl ring. As the structure–activity relationships of this ring have been previously published, it soon became clear that a 2,4,5-trisubstituted phenyl ring was required for optimum activity.

An extensive program of activity optimization resulted in the synthesis of a 2-phenyl-5-trifluoromethylpyrizadinon peroxidizing herbicide with excellent broadleaf weed control, and soybean tolerance when applied postemergence.

Concluding remarks

We have described the discovery of three new herbicides and one fungicide through a chemical approach, using the synthesis of heterocyclic compounds. As shown in the cases above, chemical approaches must be effective searching methods to generate novel bioactive molecules. From now on, new agrochemicals which are much safer as well as more efficient will be desired and various heterocyclic compounds will play a major part in this respect. We sincerely hope that ground-breaking drugs will be developed from a chemical approach, utilizing heterocyclic chemistry.