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Chemical crop protection research. Methods and challenges*

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Abstract: Chemical crop protection, today a well-established technology to support sustainable production of food, feed, and fiber, will continue to play an important role in agribusiness in spite of the emergence of novel biotechnological solutions. Scientific progress in chemistry, biology, and molecular biology has revolutionized the way of searching for new agrochemicals over the past decade. Requirements, primarily in terms of safety to humans and the environment, have also changed. The search for and the development of novel agrochemicals with novel modes of action, improved safety profiles, and adapted to the changing requirement of the food and feed production chain are more than ever the challenge.

INTRODUCTION

Weeds, diseases, and infestations by insects have always been major threats in the agricultural production of food, feed, and fiber, often giving rise to life-threatening periods of famine or causing serious food poisoning in vast parts of the world population. Protecting crops against these pests by chemical means dates back probably more than 4000 years and parallels the general development of agricultural practice. Extracts of plants containing pesticidal components and inorganic compounds have been used to different degrees over the years and often not in a systematic way. The first modern organic pesticides** were introduced in the early 1940s. The use of DDT as an insecticide, the plant hormone-based phenoxy-acetic acid derivatives as herbicides, organophosphates, and some time later the carbamates as insecticides and thiram as a fungicide marked—at least in terms of the selective activity in pest control—quantum-leap progress in pest control. Some of these early pesticides have also become symbols for the potential misuse and risks associated with their widespread application on agricultural land. The publication of *Silent Spring* by Rachel Carson [1] brought pesticide use to the notice of the general public and also marked a turning point in the risk and safety evaluation of pesticide use by producers and government agencies. Pesticides are, by definition, toxic to the target organisms, i.e., weeds, plant pathogens, and nonbeneficial insects. However, some pesticides have been and still may be misused intentionally to harm people; indeed, sometimes their origin of research goes back to the development of chemical warfare (e.g., the organophosphates).

Progress in chemical crop protection has been extraordinary over the last 60 years, not only in the invention of new and selective active ingredients but also in the assessment of the behavior of these chemicals in the environment, the residues in crop plants and of their potential toxicity to man. Over the past 60 years, crop protection measures have contributed in a decisive manner to the production of food, feed, and fiber. Famine and food polluted with noxious, naturally occurring toxins have become almost unknown in the western world. With the world population still growing and the calorie intake

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**The term “pesticide” includes herbicides, insecticides, and fungicides.

growing even steeper, production of sufficient food will continue to remain a major challenge to humans. Adequate chemical crop protection can and will contribute in the future to increase the yield per hectare and help to ensure food, feed, and fiber of high quality. This is essential since arable land reserves will stay at best at the present acreage. Novel biotechnological methods to achieve the same general goals are increasingly becoming available and may become of greater importance in the future, complementing or partly replacing the pure chemical technology of crop protection [2]. We are certainly once again at the beginning of a new technological development, not only in the protection of our traditional crops, but also in the creation of novel foodstuffs [3] (e.g., "golden rice", vitamin A-containing rice [4]). This paper attempts to give a short overview of the present methods and challenges in chemical crop protection research.

CHEMICAL SCIENCES

As long as chemical crop protection methods continue to play a dominant role, organic synthetic chemistry will remain of central significance to modern crop protection research. Ever more sophisticated methods and tools to synthesize small molecules of almost any complexity are at our disposition. This rich arsenal of synthesis methods is fully exploited in today's research laboratories. Many of these modern methods lend themselves to the large-scale production of complex molecules (e.g., Fig. 1). When occurring, enantiomers or diastereoisomers are already individually investigated at the earliest stages of research. As might be expected, often only one enantiomer shows biological activity. The challenge is to produce such active enantiomers to meet the three major objectives: high performance as a pesticide at minimum application rate in the field; adequate risk assessment; and, last but not least, low production cost. About a quarter of today's known pesticides are chiral compounds, and some of the most important and largest in terms of production scale were introduced as single isomers or diastereoisomers. Examples of important developments in the field are illustrated in Fig. 2. (*R*)-metalaxyl, the well-known fungicide employed to combat oomycetes diseases in many crops and (*R*)-clodinafop-progargyl and other aryloxy-phenoxy-propionic acid-based herbicides are produced from lactic acid, an abundantly and cheaply available intermediate of the chiral pool. The herbicide (*S*)-metolachlor is synthesized by homogeneous hydrogenation of the intermediate aryl-imine using a chiral iridium catalyst, which, regarding the scale of the industrial production, must be considered a breakthrough in the use of this technique [7]. The development of the long-known Merrifield technology of peptide synthesis on resins as a more general technology in organic synthesis opened up new dimensions in the search for new agrochemicals [8]. Further, the development of new reagents and new reactions on solid supports, coupled with the development of robots and the software required to master the logistics, now allow the production of large libraries of compounds of considerable diversity. This development has prompted chemists to take a new look at the way chemistry was traditionally done in the laboratory. As a result, miniaturized, robot-adapted reaction vessels and modern analytical and purification tools (high-performance liquid chromatography, HPLC, and HPLC/mass spectrometry, MS) are being integrated in a production line to deliver large collections of compounds in parallel using almost any available synthetic method of solution-based chemistry. At the same time, theoretical chemists have progressed in developing new methods to calculate molecular descriptors and to predict molecular properties, which

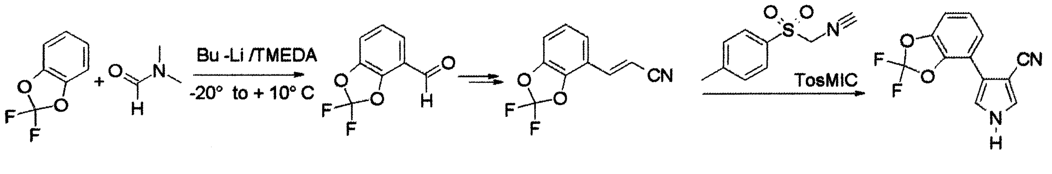

Fig. 1 Metal organic reagents in the production of fludioxonil intermediates [5].

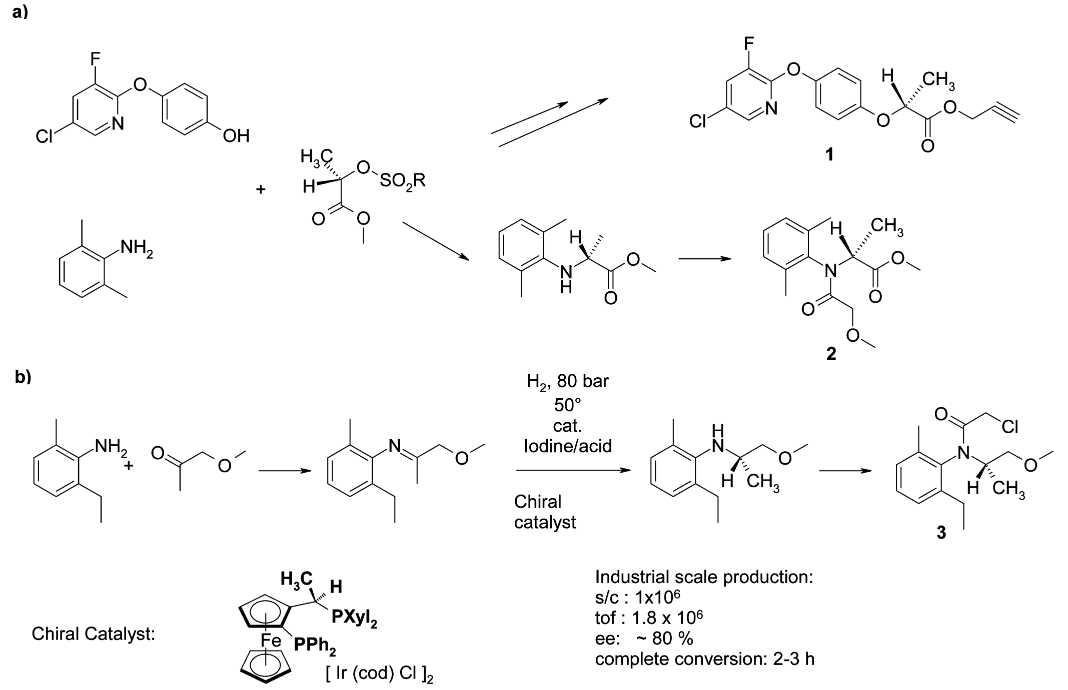

Fig. 2 Examples of the industrial-scale production of chiral pesticides: (a) (*S*)-lactic acid derivatives, reagent from the chiral pool, in the production of (*R*)-clodinafop-progargyl **1**, herbicide and (*R*)-metalaxyl **2**, fungicide [6,7]; (b) homogeneous hydrogenation using chiral catalysts in the production of (*S*)-metolachlor **3** [7].

allow, for example, the distinction between similar and dissimilar molecules or the estimation of the “drug-likeness” of candidate molecules for screening [9]. Further, methods allowing the correlation of structural properties and biological activity (structure–activity relationship, SAR) have been developed and refined. Results thereof can lead to the development of hypotheses defining the minimal structural requirements of molecules displaying biological activity. These models aid the design of new chemical libraries synthesized in the search for new leads or for the optimization of those already discovered.

This progress has meant that biology laboratories now have to provide the necessary tools to screen large numbers of compounds available only in small amounts (between micrograms and milligrams). A complete redesign of the screening operations became necessary. Screening against selected targets (enzymes, cell culture preparations, organisms in suspension cultures, leaf disks, or microplants) has been robotized and adapted for a high throughput of samples. The chemicals themselves are no longer exclusively prepared in the laboratories of the crop protection firms, but are instead increasingly purchased from firms specialized in handling large collections of compounds, from universities, or from pharmaceutical companies.

In the past, nature itself has been a very fruitful source of leads for agrochemistry. However, very often the natural products are not stable enough to be used as such, but have to be optimized to withstand the harsh conditions encountered in the field [10]. Nicotinoids based on nicotine and epibatidine, strobilurines [11] based on strobilurine A and myxothiazole, and pyrroles [12] based on pyrrolnitrin are recent examples of such novel insecticide and fungicide classes (Fig. 3). Complex natural products, such as avermectins and the spinosads [10], produced on an industrial scale by fermentation, have also successfully been introduced into the market.

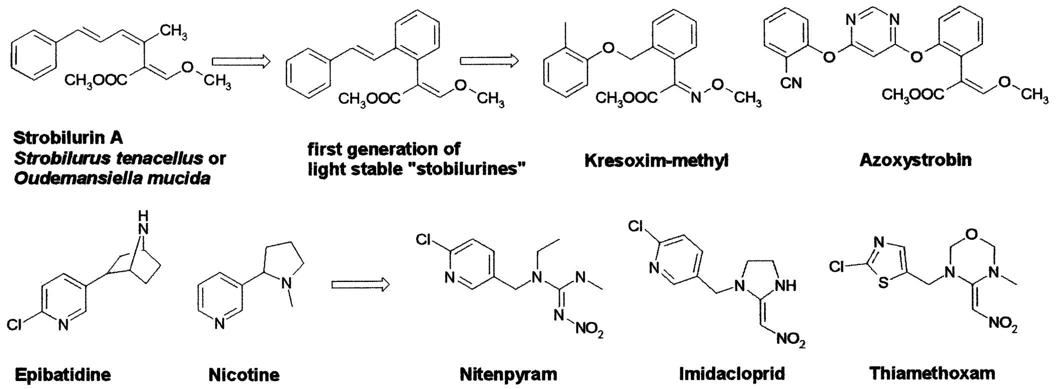

Fig. 3 Examples of the modification of natural products: strobilurine A to fungicides (e.g., kresoxim-methyl and azoxystrobin) and epibatidine/nicotine to the insecticides nitenpyram, imidacloprid, and thiamethoxam.

BIOLOGICAL SCIENCES

Screening for activity in the “natural” weed–disease–insect pest/crop complex is by nature relatively easy and relies on a long practice of growing plants (weed and crop plants) under controlled conditions in the greenhouse, propagating obligate and nonobligate diseases, and rearing insects. Screening in planta, means assessing the activity and selectivity of possible fungicides or insecticides on the host plants, and of possible herbicides on combinations of weeds and major crop plants. Today, automated procedures allow >100 000 compounds to be screened per year under quasi “near field-like” conditions, which is invaluable in the search for new leads.

Although the list of compound classes with a new mode of action is quite impressive, the search for novel modes of action remains a high priority (Fig. 4). Genomics, proteomics. and biochemistry have become an integral part of this endeavor. Present-day insight into the genomes of many plants, fungi, and insects makes it possible to actively search for novel and lethal targets in these organisms and to develop in vitro screens against the specifically selected targets. Likewise, the mode of action of leads discovered in planta can be characterized quickly as known or unknown, and in the latter case these new possibilities in biochemistry and genomics may also expedite the definition of a novel mode of action. In combination with the new tools developed in chemistry and theoretical chemistry, the search for novel targets based on genomics, proteomics, and high/ultrahigh throughput screening has become state of art in the search for novel pesticides throughout the agrochemical industry. The past unfruitful discussion on whether the one or the other modern technology might be the ultimate key to success has lead to the recognition that their integration is the key to progress.

Unfortunately, despite this progress in the search for novel leads, the rate of introduction of agrochemicals has dropped considerably over the last few years. Several reasons may be responsible for this situation:

- The state of the art of the agrochemicals already on the market is very high. Effective pest control is now possible for most crops. New formulations and application technologies have improved the performance of the already available pesticides—pesticides which, nota bene, are well investigated in terms of risk—keeping these products longer on the market.
- The development of a new agrochemical costs between $150 to 250 million and requires a minimum time of four years. Agrochemicals rank among the best-investigated chemicals in the environment. Acute and chronic toxicity assessment; dissipation in the environment by air drift, wash-off, erosion, and leaching/adsorption behavior in different soils; the influence on beneficial

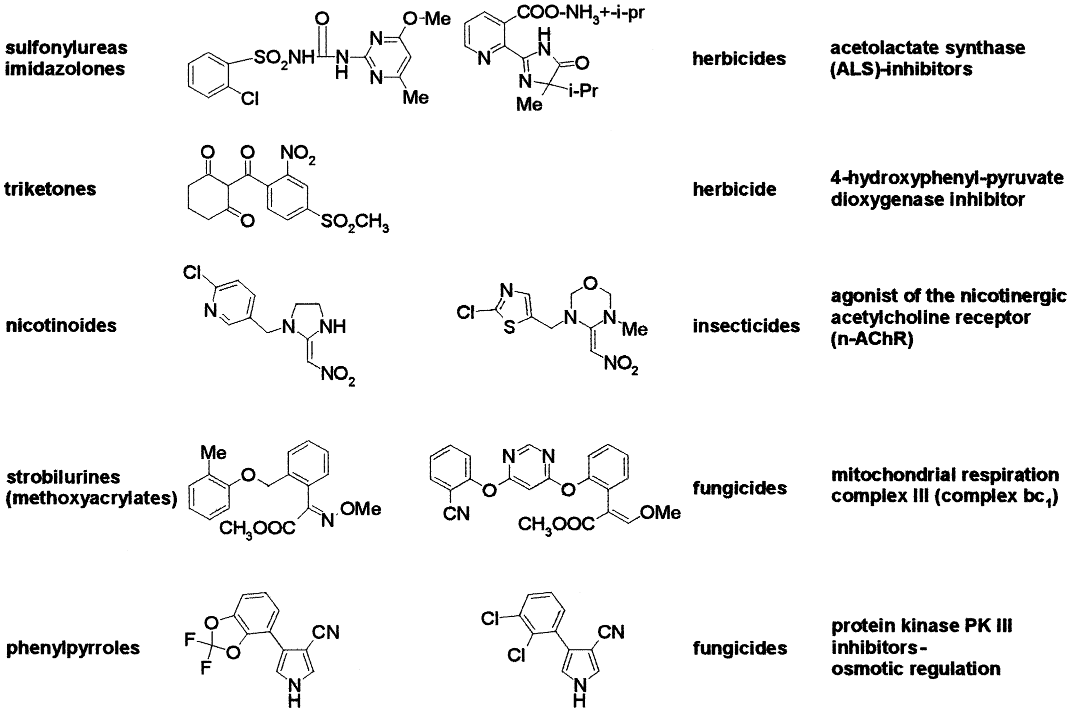

Fig. 4 Examples of important pesticide classes with novel modes of action discovered in the period 1980–2000 [2b].

organisms and microorganisms in soil and insects; the analysis of residues in food and feed; and bioaccumulation, etc. are just a few key words for the complicated process of risk assessment required to get governmental registration for the use of a pesticide.

CONCLUDING REMARKS

Looking back on the days of the first modern agrochemicals, crop protection science has made almost unprecedented progress. Chemical crop protection has become an essential tool to guarantee produce yields and quality and certainly will remain an essential element in the production of food, feed, and fiber to meet the ever-growing demands of humans. Transgenic crop plants, resistant to herbicides (e.g., glyphosate-resistant maize, soya, or cotton), are beginning to have a considerable impact on the traditional, selective herbicide technology. Although today's only commercially available insect-resistant crops (e.g., maize and cotton) express the *Bacillus thuringiensis* protein, other solutions utilizing this technology will certainly become available in the near future, as will solutions allowing the growth of disease-resistant crops. Further, crops genetically engineered to deliver improved food and feed properties will also become available. Considering their higher produce value, these will need efficient protection, ensuring the continued use of chemical pesticides and making their development key in the fight for enough food for humans.

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