Chimia 57 (2003) 725–730

ISSN 0009–4293

1λ⁴,2,4,6-Thiatriazines with Herbicidal Activity

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Abstract: 1λ⁴,2,4,6-thiatriazines were identified as a novel class of herbicides. Their interesting effects on plants as well as their uncommon structures incited further studies. In addition to the initial sulfodiimine based preparation method, a flexible synthetic route was designed giving access to a larger array of compounds. The poor initial biological activity was improved and compounds with very high herbicidal activity were identified. Thiatriazines have been found to be unique and very potent inhibitors of the biosynthesis of cellulose, which is a major component of the plant cell wall. While the precise biochemical site of thiatriazine action is not yet known, they are known to induce the formation of a non-crystalline β-1,4-glucan, as opposed to previously described herbicides which inhibit cellulose biosynthesis. Studies on the uptake, translocation and metabolism of a representative thiatriazine provided evidence for crop selectivity on the basis of differential rates of metabolism in various plant species.

Keywords: Cellulose biosynthesis · CGA 325615 · Herbicide metabolism · Sulfodiimine · Thiatriazine

Introduction

Commercial herbicides belong to a limited number of chemical classes. Even more restricted is the number of modes of action (MoA) used to control weeds. The crop protection industry seeks for lead structures with novel MoA. We would like to report on the discovery of a novel herbicidal class that inhibits a plant-specific biochemical pathway. Although known for a long time [1], 1λ⁴,2,4,6-thiatriazines were considered as chemical curiosities and had not attracted much synthetic interest until some examples distinguished themselves by their herbicidal activity. These compounds originated in Haake's group working on sulfodiimine chemistry at Marburg University, Germany. One could easily consider them as sulfur–nitrogen analogues of triazines, a known class of herbicides, but their action is obviously different.

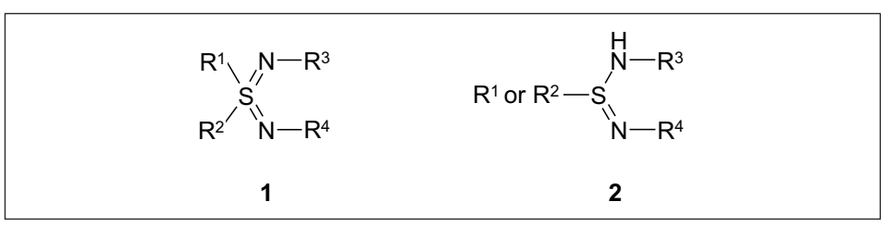
Synthesis of 1λ⁴,2,4,6-Thiatriazines Based on Sulfodiimine Chemistry

Sulfodiimines **1** are characterized by versatile functional groups. Besides acidic CH- and NH groups (R^1/R^2 = alkyl; R^3/R^4 = H) they possess nucleophilic basic nitrogen and potentially asymmetric sulfur as well. Haake has investigated sulfodiimine chemistry for many years, especially with respect to their potential use for the synthesis of novel 1λ⁶-sulfur-nitrogen heterocycles [2][3].

In certain cases, however, sulfodiimines are susceptible to C–S bond cleavage. If a positive charge is built up on sulfur either by protonation or electron withdrawing groups on one or both nitrogens (*e.g.* R^3/R^4 = acyl; sulfonyl) loss of S-alkyl/S-benzyl-groups has been observed. Thus, in protic-polar solvents and/or in the presence of other nucleophiles, quantitative conversion to sulfinamidines **2** can be achieved (Fig. 1) [2–8].

According to recent findings [6–8] this concept has been successfully used to synthesize 1λ⁴,2,4,6-thiatriazines from sulfodiimine precursors *via* different pathways.

In boiling EtOH in presence of a catalytic amount of a strong acid, sulfodiimines **3** (*e.g.* R^1 = alkyl; R^2 = benzyl) are converted to sulfinamidines **4** which undergo cyclization to **5** in either boiling DMF or in dioxane under acid catalysis. The ease of



1 **2**

Fig. 1.

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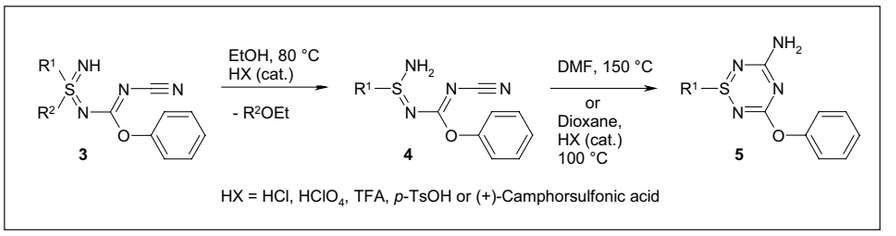
C–S bond cleavage follows the order *tert*-alkyl > benzyl ≥ *sec*-alkyl > *prim*-alkyl (Scheme 1). The *t*-butyl derivatives **7** and **8**, however, may be prepared directly from the unsubstituted sulfinamidine **6** (Scheme 2) [9].

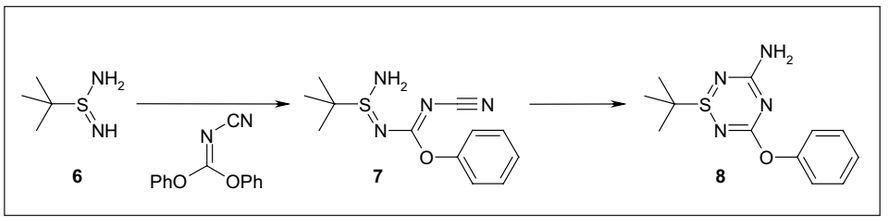
Thiophane, thiacyclohexane or thioxane-derived sulfodiimines of type **9** cyclize under acidic conditions in various solvents (CH_2Cl_2, dioxane, HOAc) to give the $1\lambda^6$,2,4,6-thiatriazinium salts **10**. These may either be isolated or further transformed into $1\lambda^4$-thiatriazines of type **11** with a functionalized alkyl substituent, under C–S bond cleavage, simply by heating in DMF, dioxane or acetone with the appropriate nucleophiles (Scheme 3). Iodinated compounds **11** can easily undergo further substitution of the iodide with a whole range of nucleophiles. Furthermore, $1\lambda^4$-thiatriazines **5**, **8**, and **11** as well as sulfinamidines **4** and **7** may undergo nucleophilic displacement of the phenoxy-group, addition of heterocumulenes to NH_2, or oxidation on sulfur with $KMnO_4$ to give the corresponding S-oxides.

Since the sulfur atom is asymmetric, it was possible for the first time to resolve examples of **5** by HPLC-technique on a β-cyclodextrin (ChiraDex®) column. This offered the possibility to study stereochemical aspects [8].

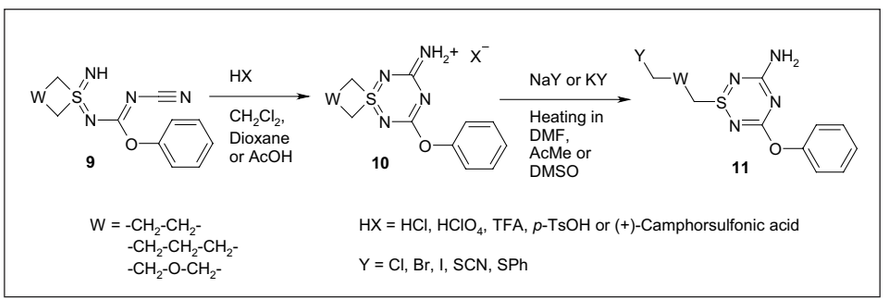
Herbicidal tests revealed that $1\lambda^4$,2,4,6-thiatriazines with C_4–C_8 alkyl substituents on sulfur as well as NH_2 at C-3 and a phenoxy group at C-5 were quite favorable. Thus **12** and **13** became the first lead structures (Fig. 2).



Scheme 1.



Scheme 2.



Scheme 3.

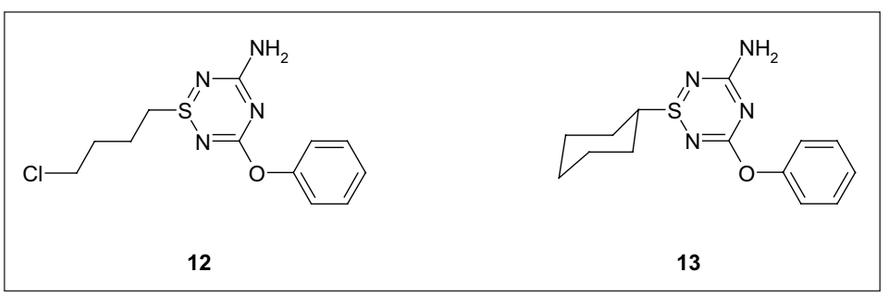


Fig. 2.

New Synthetic Approach to $1\lambda^4$,2,4,6-Thiatriazines

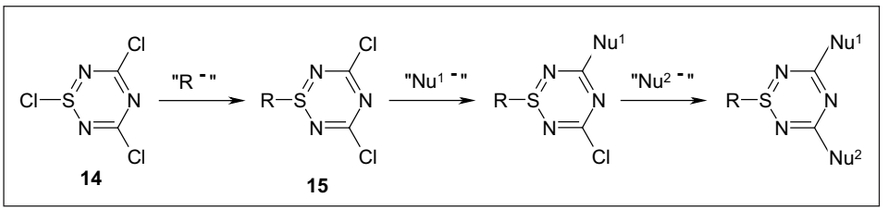
The synthetic strategy shown above (Schemes 1–3) has led to the discovery of innovative compounds with interesting herbicidal activities. The symptoms induced on plants as well as their structural originality make these thiatriazines a very attractive class of compounds. A broad structural variation was desired in order to have a grasp on the parameters important for the biological properties (activity, selectivity…). It was decided to keep the heterocyclic system constant, as this was a unique characteristic, but to have a shorter and more flexible access to the final compounds, allowing for more variations on the substituents.

Few thiatriazines with a tetravalent trisubstituted sulfur atom have been described in the literature and compounds belonging to this chemical class with a carbon-based substituent at the sulfur are even much fewer [7][10–13]. Furthermore, the strategies used to access them were limited in their applicability. In each of those cases, the carbon–sulfur bond was already present in the starting material, which means that any change of the 1-substituent would necessitate a complete resynthesis.

In analogy to the preparation of the classical triazine herbicides (consisting of a symmetrical triazine ring with two alkylated amino substituents and a third alkoxy, alkylthio or chloro substituent) from cyanuric chloride, trichlorothiatriazine (**14**) (Scheme 4) would be an interesting building block if the three chlorine atoms could be replaced selectively and successively by a large variety of substituents or their precursors. This heterocyclic building block has already been described in the literature [14] but, despite its huge synthetic potential, has been used only sparingly. The viability of this approach depended on the possibility of introducing the substituents, as shown in Scheme 4. All the attempts described in the literature for substituting the chlorine atoms used heteroatomic nucle-

ophiles, like alcohols, mercaptans or secondary amines or their metallic salts [15–18]. These studies also showed that the chlorine at the sulfur atom was the most reactive one towards these nucleophiles.

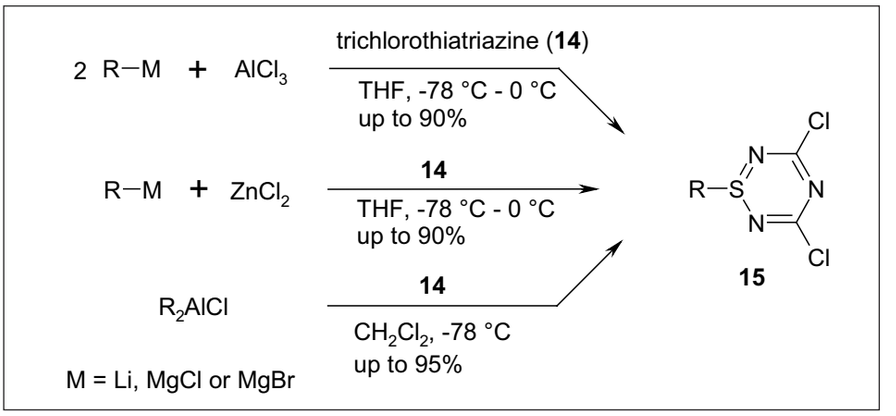
One challenging problem was the unprecedented introduction of a carbon-based substituent on the sulfur atom of trichlorothiatriazine. As the chlorine at the 1-position is the most reactive, this reaction had to be carried out on **14**, potentially leading to dichlorothiatriazines **15** with a carbon-based substituent at the sulfur. Due to the electrophilic nature of the sulfur in **14**, various organometallic reagents were tried.



Scheme 4. New strategy for the preparation of substituted thiatriazines

Introduction of an Alkyl Substituent

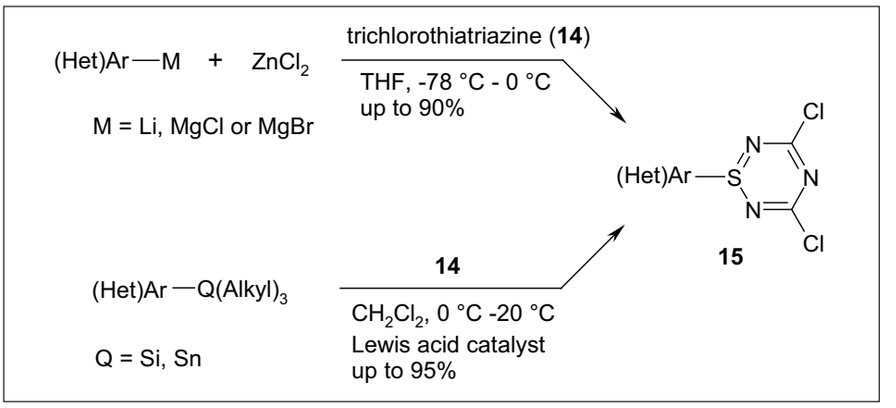
The use of alkyllithium or alkylmagnesium reagents at low temperature yielded none or little (<25%) of the corresponding 1-alkylated thiatriazines **15**. The modification of the reagents by addition of zinc chloride or aluminum chloride, or the use of preformed chlorodialkylaluminum however led to much higher yields (up to 95%) and made this approach to a valuable preparation method (Scheme 5). The stability of these derivatives was good to acceptable in most cases.



Scheme 5. Introduction of an alkyl substituent

Introduction of an Aryl or Heteroaryl Substituent

In a similar way, an aryl or heteroaryl group can be easily attached to the sulfur atom by replacing the chlorine atom when the corresponding organolithium or organomagnesium species is treated with zinc chloride prior to reaction with trichlorothiatriazine (Scheme 6). The coupling of aryl or heteroaryl groups can also be obtained under very mild reaction conditions (0 °C – 20 °C) from the corresponding preformed trialkylsilyl- or trialkylstannyl derivative in presence of a catalytic amount of Lewis acid through an *ipso*-thia-desilylation or -destannylation reaction.



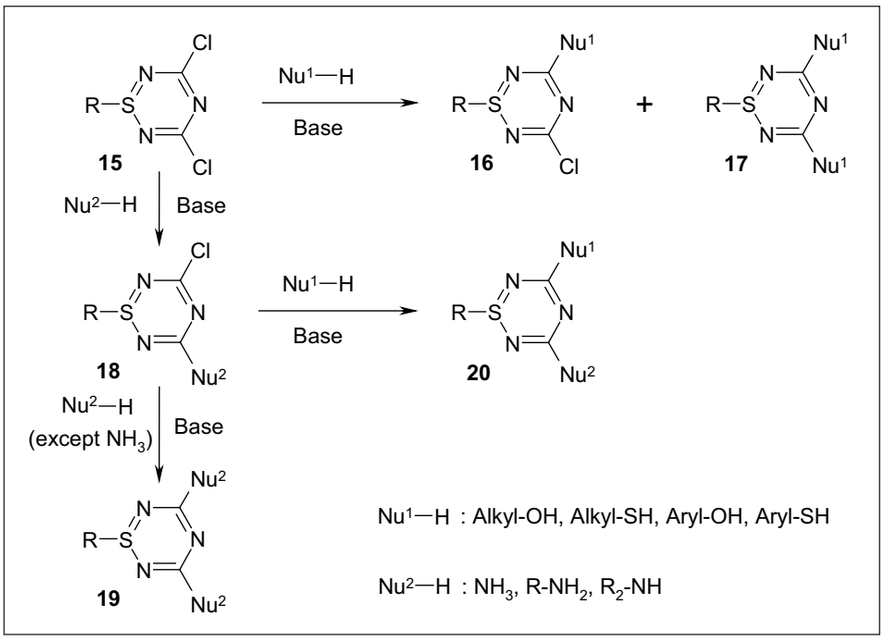
Scheme 6. Introduction of an aryl or heteroaryl substituent

Substitution at the Other Two Positions

The 1-substituted-3,5-dichlorothiatriazines **15** react further with alkyl alcohols, phenols, mercaptans, usually non-selectively, leading to mono- and disubstitution products **16** and **17** (Scheme 7). In contrast, the substitution with amines is more selective since the introduction of the first amino group deactivates the last substitution. In case of ammonia, disubstitution to **19** does not occur and the mono amino derivatives **18** are formed almost quantitatively so that products **20** with Nu^1 = phenoxy and Nu^2 = NH_2 are best made by treating the dichloro-derivatives **15** with excess ammonia prior to reaction with phenoxides [19]. The stability of these systems facilitates further modification of the trisubstituted thiatriazines **20**.

Structural and Stereochemical Aspects

X-ray structure determination of $1\lambda^4$,2,4,6-thiatriazines shows the non-planarity of the heterocyclic system. The sulfur atom is tetragonal and points out of the average plane formed by the five other atoms. Its substituent is in pseudoaxial position, the so-formed bond making almost a right angle with the average plane (Fig. 3). In cases where the 3- and 5-substituents are different, the sulfur atom is an asymmetric center. It is configurationally stable. In the case of CGA 325615 (compound **20** with R = *c*-hexyl, Nu^1 = pentafluorophenoxy and Nu^2 = NH_2), the enantiomers were separated on a chiral column. No racemization was observed, even after prolonged storing at room temperature. Only one enantiomer showed herbicidal activity.



Scheme 7. Substitution of the 3- and 5-positions

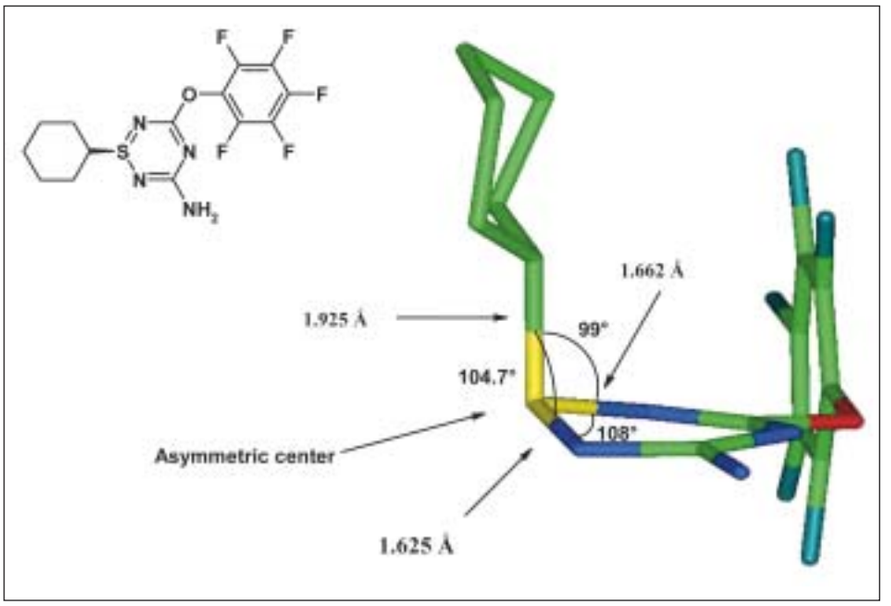


Fig. 3. X-ray structure of an enantiomer of CGA 325615

Structure–Activity Relationship

Many of the thiatriazines reported here display pre- and post-emergent herbicidal activity. Variation of the three substituents around the heterocycle has led to the following results.

In order to attain a good level of weed control, an amino function is preferred (**20** with $Nu^2 = NH_2$).

The herbicidal activity of the derivatives **20** is strongly increased on going for Nu^1 from the naked phenoxy- to the 2,5-difluorophenoxy- and further to the pentafluorophenoxy- groups, while keeping both of the other substituents constant.

The nature of the sulfur substituent modulates the activity level as well as the spectrum of controlled weeds and the selectivity for crops.

For example, the *para*-chlorophenyl-analog of CGA 325615 is selective in paddy rice (excellent control of *Echinochloa*, in transplanted rice under paddy field conditions at 7.5 g active ingredient/ha with pre- to early post-emergence application) and the *n*-heptyl-analog has a wide broadleaved and grassy weeds spectrum with a good selectivity in maize at 100 g active ingredient/ha in pre-emergent application.

Biochemical Studies of Thiatriazines

Studies on the herbicidal mode of action revealed that the thiatriazines affect the biosynthesis of cellulose. Cellulose (β-1,4-glucan) is a major component of the cell wall of plants, where the glucan chains are deposited as parallel arrays to form semi-crystalline microfibrils that provide unique properties to plant tissues such as tensile strength and flexibility. Disruption of cellulose biosynthesis, either by genetic mutation or chemical inhibition, is known to impair plant growth and cause severe disorders in the development of the plant architecture [20]. Observations in the greenhouse revealed that the thiatriazines evoke novel symptoms on susceptible plants. Upon post-emergent application, grass species developed fragile culms and were impaired in growth and development of the root system. Dicotyledonous plants exhibited a characteristic swelling of the stem basis, splitting of stems and rapid wilting. In laboratory studies with *Arabidopsis thaliana* (thale cress) seeded onto an agar-solidified nutrient medium containing CGA 325615, seedlings developed as stunted plants with brown and swollen roots at a concentration of about 1 nM, while germination was not inhibited up to 10 nM. The most sensitive visual effect, however, could be elicited on the root tips that displayed detectable symptoms upon direct exposure to CGA 325615 at concentrations as low as 0.1 nM. These symptoms included cessation of root cell elongation, radial swelling of the root tip and formation of swollen root hairs. Microscopic examination of suspension cultures of plant cells from various species also revealed a characteristic expansion of cells with an increase in diameter up to three-fold after a few days of exposure to nanomolar concentrations of thiatriazines. While some of the effects of thiatriazines on root and suspension cell morphology are reminiscent of those induced by mitotic disrupter herbicides, *e.g.* dinitroanilines, the thiatriazines did not affect the progression of cells through the mitotic stages as studied in the root apical meristem of *Vicia faba*.

Disruption of cellulose synthesis by thiatriazines could be demonstrated by studies on the incorporation of ^{14}C-labeled glucose into the cellulose fraction of cell walls of suspension cultured cells from

soybean, tomato and *Ocimum basilicum* (sweet basil). The IC_{50} value for the inhibition of cellulose biosynthesis in soybean cells ranged from 2.5 nM for the biologically most active thiatriazine, CGA 325615, to > 1 μM for **13** (Fig. 2). There was generally a very good correlation between inhibition of cellulose biosynthesis in the cell culture system and herbicidal activity under greenhouse conditions among a broad range of thiatriazines.

Attempts were made to define the biochemical site of thiatriazine action more precisely. Cell wall fractionation studies following incorporation of ^{14}C-labeled precursors revealed that the formation of the other polysaccharide constituents of the cell wall, *i.e.* xyloglucan and pectin, and of cell wall glycoproteins was not diminished by thiatriazines. However, thiatriazine treatment was found to cause an aberrant accumulation in the cell wall of a glucan fraction with solubility properties different from those of native cellulose. Furthermore, protoplasts derived from plant cells by enzymatic removal of the wall material failed to regenerate a cell wall in the presence of CGA 325615, but produced an amorphous material tentatively identified as β-1,4-glucan. Subsequent investigations with CGA 325615 in developing cotton (*Gossypium hirsutum*) fibers employing methylation analysis and enzymatic digestion studies have confirmed the formation of a β-1,4-linked glucan whose unusual solubility properties may be explained by its low crystallinity and strong association with proteins [21]. In the same work, these proteins were identified as the glucosyltransferases, GhCesA1 and GhCesA2, that have previously been shown to form part of the cellulose synthase complex in cotton [20]. This is a large plasma membrane-bound multi-subunit enzyme complex that comprises, besides other proteins, multiple glucosyltransferase subunits. The cellulose synthase complex is thought to mediate the processes involved in β-1,4-glucan chain polymerization utilizing the monosaccharide donor, uridine 5'-diphospho-α-D-glucopyranose (UDP-glucose), assembly of glucan chains to crystalline cellulose microfibrils and their deposition in the extracellular matrix.

Interestingly, our observations of the thiatriazine-effects on *Arabidopsis* growth and morphogenesis were very similar to the phenotypes exhibited by known mutants with a deficiency in cellulose formation. In particular, the *Arabidopsis* mutant *rsw1* (radial swelling phenotype) displays a strikingly similar symptomology, is impaired in the formation of crystalline cellulose and produces a non-crystalline β-1,4-glucan. This defect is due to a point mutation in the gene *AtCesA1* which encodes a glucosyltransferase subunit of the *Arabidopsis* cellulose synthase complex [22].

The findings described above strongly suggest that thiatriazines interfere with the formation or function of the cellulose synthase complex. The exact biochemical site of action, however, remains to be determined. Unfortunately, attempts to develop an experimental system derived from plants that is suitable for the characterization *in vitro* of cellulose biosynthesis inhibitors have been unsuccessful up to now [20]. Other processes of cellular metabolism such as photosynthesis, respiration, and the biosynthesis of lipids, proteins and DNA were not affected. In particular, enzyme activities involved in the synthesis and utilization of UDP-glucose were not inhibited by thiatriazines, which shows that inhibition of cellulose synthesis is not due to disruption of supply with activated glucose.

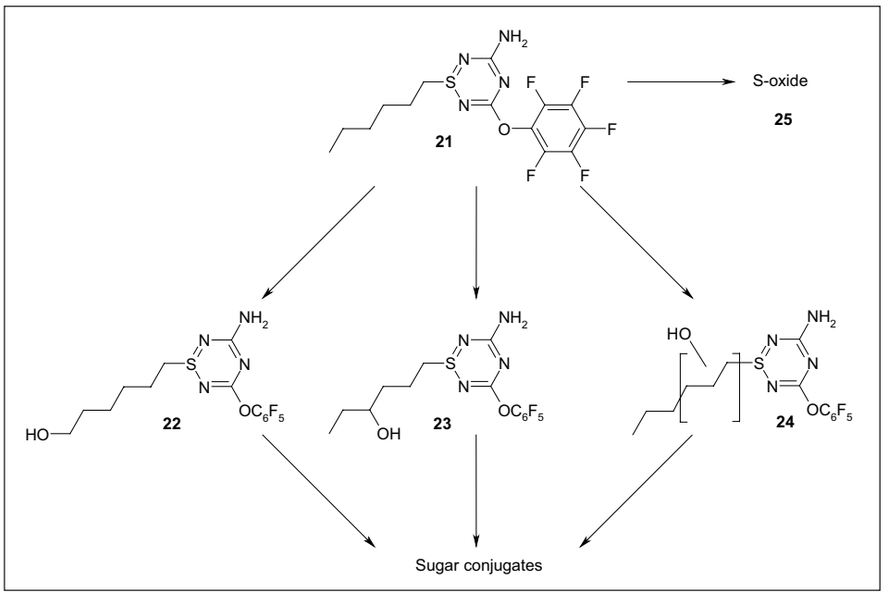
Comparison of Thiatriazines to Other Cellulose Biosynthesis Inhibitors

Cellulose biosynthesis is a potentially attractive target for herbicide action, and several inhibitors of the process have been identified, the two most well known being 2,6-dichlorobenzonitrile and isoxaben [23]. The thiatriazines described herein, however, differ in various respects from other known cellulose biosynthesis inhibitors. The most striking biochemical property of the thiatriazines is their exceptionally high potency. IC_{50} values measured in our laboratory for inhibition of cellulose synthesis in suspension-cultured plant cells were several orders of magnitude higher, in comparison to CGA 325615, for 2,6-dichlorobenzonitrile (3.6 μM in soybean cells), isoxaben (0.9 μM), and the two more recently discovered herbicides, triazofenamide (0.1 μM) [24] and 5-*tert*-butyl-carbamoyloxy-3-(3-trifluoromethyl)-phenyl-4-thiazolidinone (0.2 μM) [25]. Further distinction comes from the finding that 2,6-dichlorobenzonitrile does not induce the formation of non-crystalline β-1,4-glucan in developing cotton fibers [21]. Instead, 2,6-dichlorobenzonitrile has been postulated to inhibit the formation of the plasma membrane sterol derivative, sitosterol-β-glucoside which is thought to serve as a primer for cellulose synthesis [26]. Finally, *Arabidopsis* mutants displaying high levels of resistance to isoxaben and to 5-*tert*-butyl-carbamoyloxy-3-(3-trifluoromethyl)-phenyl-4-thiazolidinone due to recently identified amino acid substitutions in the cellulose synthase protein isoform AtCesA3 [27] were not resistant to CGA 325615. While this provides very strong evidence for the identity of AtCesA3 as the binding site of isoxaben and the thiazolidinone, it does not necessarily preclude that thiatriazines interact with another site of this protein or other cellulose synthase isoform(s) encoded by the *CesA* multigene family [20].

Fate of Thiatriazines in the Plant – A Case Study

Differences in the susceptibility of various plant species to a particular herbicide are often due to differential rates of metabolic inactivation of the active ingredient [28]. For many classes of crop-selective herbicides, differential metabolism constitutes the major single factor for crop tolerance rather than others such as differences in herbicide uptake, translocation or sensitivity of the target site. To investigate the mechanisms possibly involved in the observed selectivity in wheat of the post-emergence applied thiatriazine CGA 354383, its fate in plants was investigated using an n-hexyl[5,6-^3H]-labeled preparation of CGA 354383 (**21**). These studies provided some evidence to conclude that rapid metabolism of **21** is the basis for the tolerance of this thiatriazine in wheat. In the plant species investigated, *i.e.* winter wheat (*cv.* 'Runal' and 'Arina') and the grass weed *Alopecurus myosuroides*, and in cell suspension cultures of tomato, soybean and *O. basilicum*, the metabolic pathway of **21** consisted in an oxidative transformation at the n-hexyl substituent, primarily in the ω–position (**22**; Scheme 8). Metabolites hydroxylated at other positions of the aliphatic side chain (**23**, **24**) and the tentatively identified S-oxide (**25**) were also formed. The hydroxylated products did not accumulate to appreciable amounts but underwent extensive conjugation to carbohydrate (hexose) moieties and secondary conjugations with unidentified residues. Volatile metabolites and non-extractable residues were not produced to detectable amounts. Chemically synthesized **22**, **23** and **25** have been found to be herbicidally inactive, and inhibited cellulose biosynthesis in suspension-cultured soybean cells at concentrations several orders of magnitude higher than **21** (*e.g.* $IC_{50} \approx 800$ nM for **23** *vs.* 5.3 nM for **21**). Thus, the metabolic routes of **21** afford an efficient detoxification, though it remains unclear whether this is due to lower intrinsic activities of **22**–**24** or to their rapid sugar conjugation in the plant cell. Interestingly, while no significant differences in the rates of metabolism could be detect-

ed in the root tissues of wheat and *A. myosuroides*, striking differences were found in the leaves of these species. In wheat leaves, 62% of the absorbed **21** was degraded 48 h after foliar application, but only 21% had been metabolized in *A. myosuroides*. Uptake of **21**, either through the roots or after foliar application of the formulated product in the presence of a non-ionic surfactant, was not significantly different between wheat and *A. myosuroides*. Translocation of foliarly absorbed **21** to the root system was marginal, <0.5% within 48 h, in both plant species. On the other hand, **21** was readily distributed throughout the plant *via* the transpiration stream after root application in a hydroponic system. In conclusion, the present results provide some explanation for the observed selectivity in wheat of post-emergence applied **21**, and possibly other thiatriazines, on the basis of their differential metabolism in the crop and in susceptible weeds.



Scheme 8. Proposed pathways of CGA 354383 (**21**) metabolism in plants. Metabolites **22** and **23** were identified by LC/MS and co-chromatography with synthetic reference standards. **24** was tentatively identified by LC/MS only, and **25** by co-chromatography with a synthetic reference. Sugar (hexose) conjugates undergo partial secondary conjugation to unidentified moieties.

Conclusion

Herbicidal activity was found for $1\lambda^4$,2,4,6-thiatriazines through random screening. Using different chemical strategies, it was possible to design very active compounds. Biochemical studies showed that they affect the biosynthesis of cellulose.

Acknowledgement

The authors would like to thank the following colleagues for their contributions to the work described herein: Drs. R. Fonné-Pfister, V. Oberhauser, K. Ramsteiner.

Received: September 17, 2003

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