Synthesis of New Substituted 1λ⁴-1,2,4,6-Thiatriazines

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In a company, which is involved in life sciences, the search for biologically active compounds is a very important task. The biological screening of compounds resulting from a rational design and random substances are complementary.

In our screening, substances showing interesting herbicidal activity and unusual chemical structures have been detected. Furthermore, their chemical potential and their variation possibilities prompted us to study the class of 1λ⁴-1,2,4,6-thiatriazines.

The molecules described in this work are composed of a six-membered heterocyclic system containing one atom of sulfur, two atoms of carbon and three atoms of nitrogen distributed in a symmetrical way (Figure 1). The numbering of the system starts at the sulfur atom. The latter is bound to two nitrogen atoms and is of the tetravalent-trisubstituted state, which is explained by the term 1λ⁴. The heterocycle is pseudoaromatic and is substituted at the positions 1, 3 and 5. The molecules of interest bear a carbon based substituent at the sulfur and amino, aryloxy or alkoxy groups at the remaining positions.

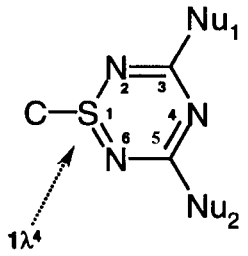


Figure 1. 1-Carbo-1λ⁴-1,2,4,6-thiatriazines

1. Syntheses of 1-Carbo-1λ⁴-1,2,4,6-thiatriazines; State of the Art.

Before the present work there were only a few reports in the literature regarding this type of compound.

The three first 1-carbo-1λ⁴-1,2,4,6-thiatriazines described in the literature have been synthesized by J. Goerdeler *et al.* in 1954 starting from metal alkanethiolates and *N*-bromobenzamidine (Scheme 1) [1].

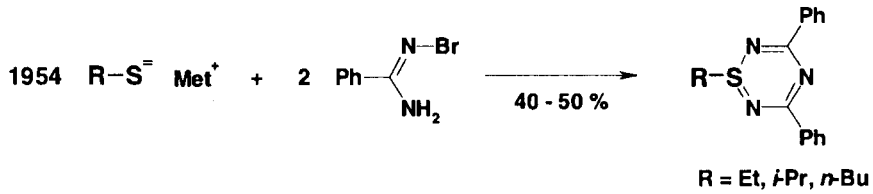
In 1962, J. Goerdeler *et al.* described two other syntheses where in one case reaction between *N*-alkanesulfenylamidines and *N*-bromoamidines resulted in diacylimidoylalkanesulfinamidines which were cyclized to the thiatriazine system where all the substituents are carbon based (Scheme 2) [2]. In the other case, *N*-benzenesulfenyl-*N'*,*N'*-diphenylguanidine was reacted with *N*-bromobenzamidine and the resulting substituted benzenesulfinamidine was cyclized to the thiatriazine system in about 25% yield (Scheme 3) [3].

In 1982, L. N. Markovskii *et al.* published the synthesis of substituted dihydrothiatriazines where phenylsulfenyl chloride reacted with *N*-chloroimines to substituted benzenesulfinimidoyl chlorides, which were cyclized with *N*-phenylbenzamidine in less than 30% yield (Scheme 4) [4].

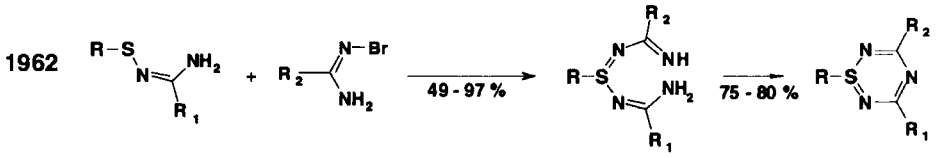
In 1988, W. Ried *et al.* synthesized 3-amino-1-carbo-1λ⁴-1,2,4,6-thiatriazines starting from *N*-cyanoimino derivatives and diorganylsulfodiimides, where the sulfur is of the hexavalent tetracoordinated state (Scheme 5) [5]. In this approach, the intermediate sulfodiimide having a *N*-cyanoimidoyl substituent on a nitrogen is submitted to thermal and acidic conditions, which induce the formation of the heterocycle and the loss of one of the substituents at the sulfur. The yields of product obtained by this method are usually not very high (27-73%).

The same year M. Haake *et al.* published the synthesis of 3-amino-1-carbo-1λ⁴-1,2,4,6-thiatriazines substituted with either phenoxy or amino at the 5-position, using a similar strategy (Scheme 6) [6]. They used diorganylsul-

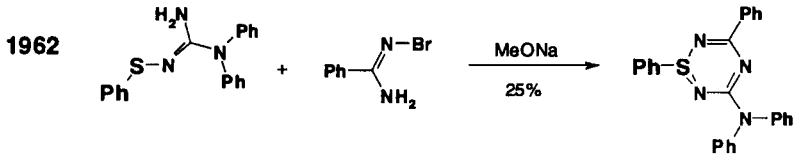
Scheme 1



Scheme 2



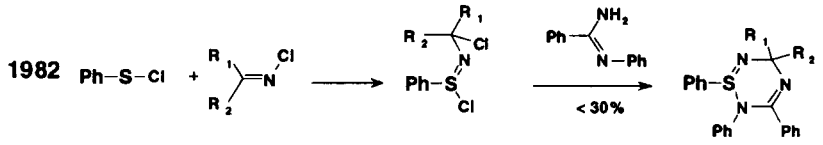
Scheme 3



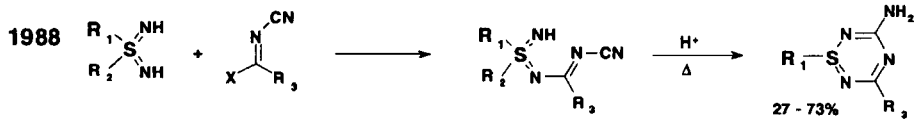
fodiimides and diphenyl *N*-cyanoimidocarbonate. The resulting substituted intermediate sulfodiimide was then either directly cyclized or treated with an amine prior to cyclization. Yields inferior to 60% are usually obtained.

There are only a few methods available for the preparation of 1-carbo-1λ^4-1,2,4,6-thiatriazines and even if the synthetic strategies employed differ from one to another, some common characteristics can be observed:

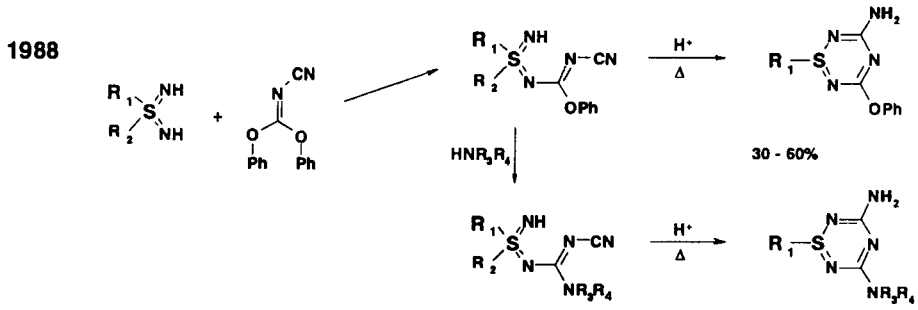
Scheme 4



Scheme 5



Scheme 6



• In all the known syntheses, the carbon based substituent is bound to the sulfur before the formation of the heterocycle.

• The choice of the substituents on the heterocycle has to be made very early in the synthesis.

• The starting materials used for these syntheses have usually been produced by a multistep process, which can be cumbersome.

• The scope of these methods may be very limited.

A more practical synthesis of 1-carbo-1λ⁴-1,2,4,6-thiatriazines would be very welcome.

2. Trichlorothiatriazine as Building Block for New Synthesis?

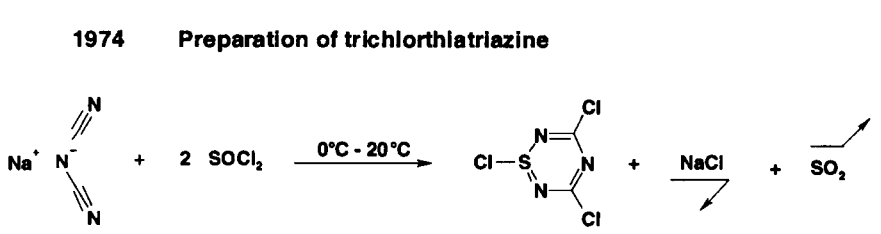
A look in the literature shows that the synthesis of 1,3,5-trichloro-1λ⁴-1,2,4,6-thiatriazine has been described and patented over 25 years ago by W. Schramm *et al.* (Scheme 7) [7]. This molecule is the first example of this type of heterocycle where the sulfur does not carry a carbon atom. This compound can be very easily prepared in one step, starting from inexpensive sodium dicyanamide and thionyl chloride in good yields. Trichlorothiatriazine is a stable compound if kept away from moisture. It is distillable (bp: 100°C under 20 mbar) and crystallizes on standing (mp: about 40°C). It can be stored for extended periods of time (several years) without noticeable decomposition.

The synthetic potential of this molecule is huge as its heterocyclic nucleus carries three chlorine atoms which can be considered as three leaving groups and could be replaced by different nucleophiles. Moreover the 1-position of the heterocycle is much more activated than the 3- and 5-positions, so that regioselectivity in the replacement of the chlorine atoms should be attainable. These elements made the foundation of a new synthetic strategy toward substituted 1-carbo-1λ⁴-1,2,4,6-thiatriazines starting from trichlorothiatriazine (Scheme 8). The first step would be the replacement of the chlorine at the sulfur. It would need a reagent with a nucleophilic carbon atom. The resulting dichlorothiatriazine would be subjected to stepwise replacement of the other chlorine atoms by adequate nucleophiles (heteroatom based, in our case).

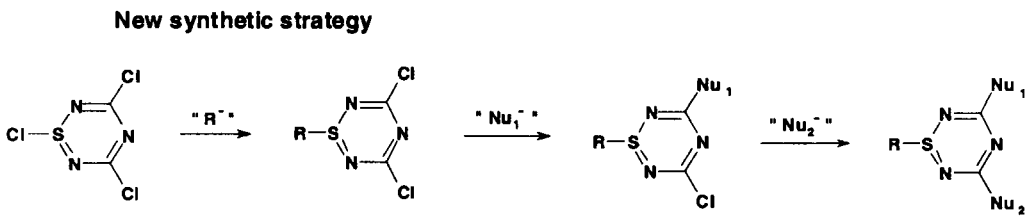
3. Substitution at the Sulfur Atom.

No reaction where the chlorine at the sulfur of trichlorothiatriazine has been replaced by a carbon atom was known, but its substitution with amines, though restricted to sterically hindered secondary amines has been described by W. Schramm *et al.* (Scheme 9) [8]. Selective monosubstitution was observed but further substitution of the other chlorine atoms could be obtained with a few amines, simple alcoholates and mercaptides [8-12].

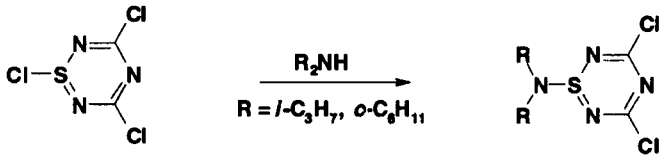
Scheme 7



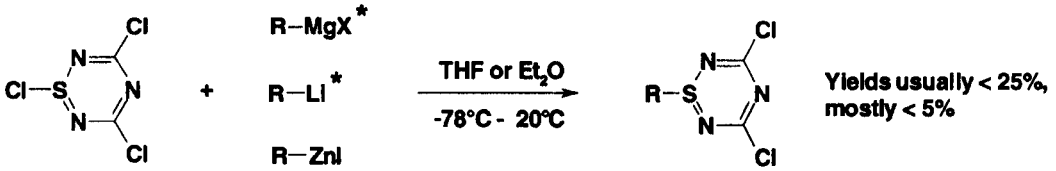
Scheme 8



Scheme 9



Scheme 10



* also in combination with metal salts like $CeCl_3$, $CrCl_3$, CuCN, $MnCl_2$, (CuBr,Me_2S)

A. Introduction of sp^3 Carbon at the Sulfur.

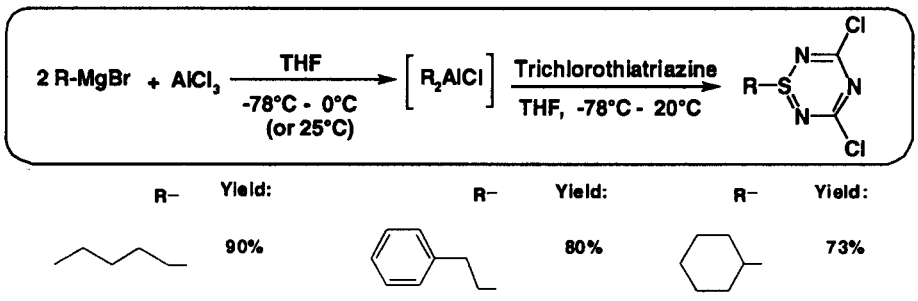
The substitution of the 1-chlorine of trichlorothiatriazine by a carbon atom had never been reported. Nucleophilic carbon derivatives would be needed and the first trials were made by using organometallic reagents (Scheme 10). In a first screening alkylmagnesium bromides or chlorides and alkyllithiums were tested. They were treated with trichlorothiatriazine at -78°C, then allowed to warm up to 20°C. In other trials, the same organometallic derivatives were first pretreated with various metal salts like cerium(III) chloride, chromium(III) chloride, copper cyanide, copper(I) bromide-dimethylsulfide complex or manganese(II) chloride prior to reaction with trichlorothiatriazine, in order to modulate their reactivity. Alkylzinc iodides have also been tested. Although the desired compounds were obtained in some cases, the first results were rather disappointing with yields generally inferior to 25% and mostly inferior to 5%.

Use of Organoaluminium Derivatives.

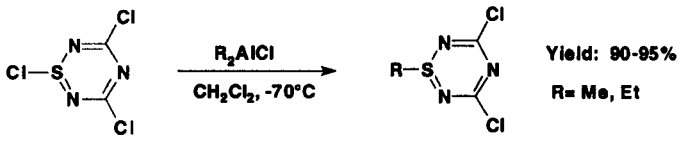
When a solution of alkyl magnesium bromide was treated with half an equivalent of aluminium chloride at low temperature followed by warming up to 25°C prior to the reaction with trichlorothiatriazine (1 equivalent relative to aluminium chloride), the yield of *S*-alkylated thiatriazine increased dramatically to 90% (yield of isolated product based on trichlorothiatriazine) (Scheme 11).

It is reasonable to assume that under these conditions an intermediate dialkylaluminium chloride, which could be the reactive species is formed. The composition of the reaction mixture at this stage has not been analyzed and it was not known if magnesium halide does play a role in the reaction. To verify this assumption, trichlorothiatriazine has been

Scheme 11



Scheme 12



treated with pure dimethylaluminium chloride or diethylaluminium chloride (Scheme 12). The reaction mixture was free of magnesium salts. The alkylation proceeded smoothly at very low temperature to form the corresponding *S*-alkylated thiatriazines in yields of 90% to 95% (isolated products).

As only one equivalent of trichlorothiatriazine is used for each equivalent of aluminium chloride, the yield of product relative to the involved alkyl group is less than 50%. It is not increased by the use of more trichlorothiatriazine. This situation is acceptable in many cases, but could be a serious drawback in case of highly valuable groups to be transferred.

Use of Organozinc Derivatives.

Later it has been found that treating the organomagnesium halide or organolithium with one equivalent of zinc chloride (instead of aluminium chloride) at low temperature, followed by warming up to 25°C permitted the substitution of the *S*-chlorine in usually better yields relative to the organic group (Scheme 13).

Even bulky groups participate in the reaction. The limitation observed in the use of organometallics is sometimes the difficulty to generate such reagents carrying functional groups.

Use of Organozirconocene Derivatives.

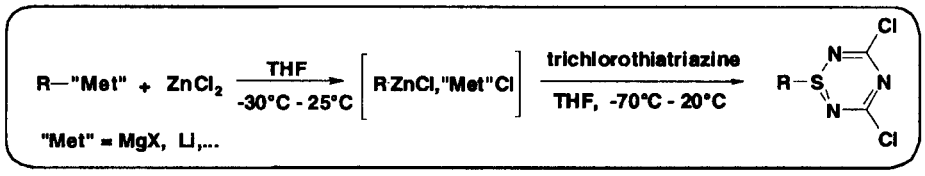
By using milder organometallic reagents or reagents whose formation can be performed under milder conditions, sensitive functional groups may be tolerated.

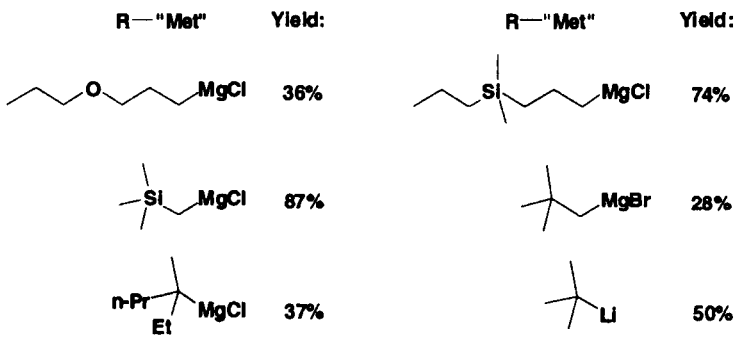
Alkylzirconocene derivatives, which can be prepared from olefins (preferentially α-olefins) and zirconocene hydrido chloride (Schwartz' reagent) may contain ester functions or halides otherwise not compatible with the use or the formation of alkyllithiums or alkylmagnesium halides. They react with trichlorothiatriazine at low temperature to yield the corresponding 1-alkyl-3,5-dichloro-1λ⁴-1,2,4,6-thiatriazines (Scheme 14).

Another advantage of this method is that easily accessible, unactivated olefins can be used as starting materials. In the case of unconjugated polyolefins, the reaction takes place preferentially at the terminal unsaturation, which is the least sterically crowded.

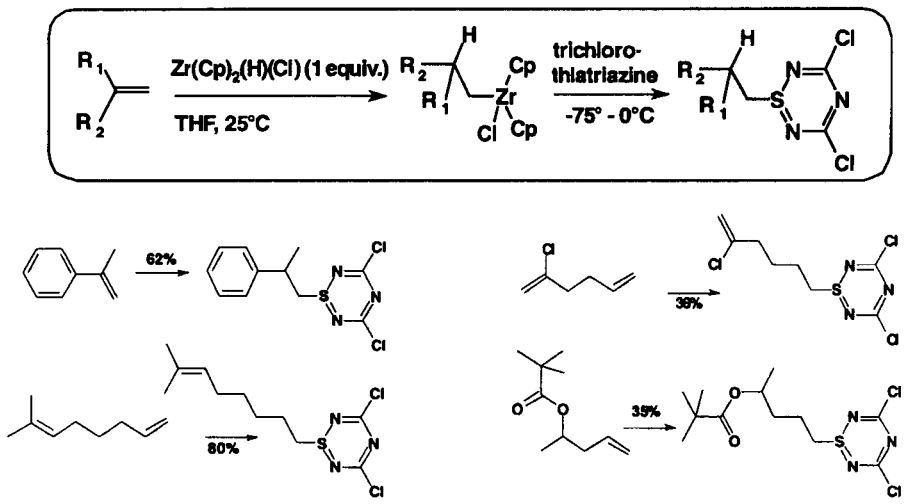
Different synthetic methods allowing the replacement of the chlorine atom at the sulfur of trichlorothiatriazine by substituents bound to the heterocycle *via* a sp^3-hybridized carbon have now been made available.

Scheme 13





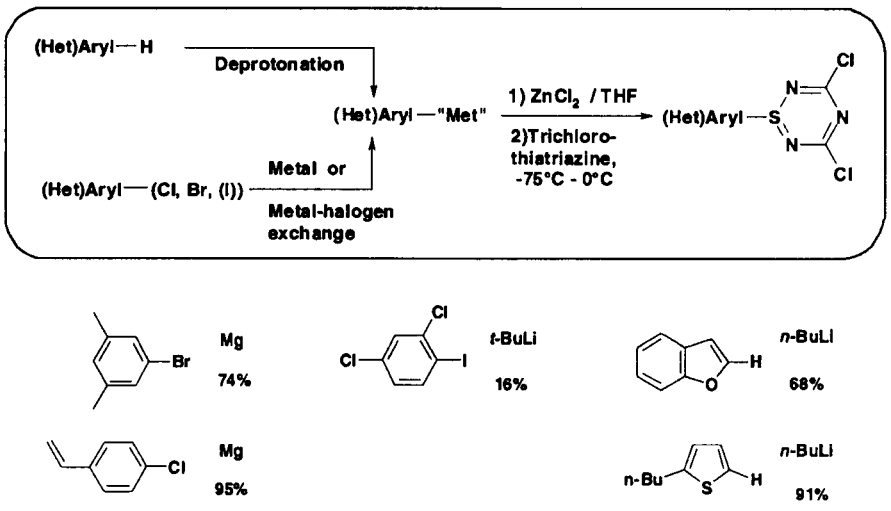
Scheme 14



B. Introduction of sp^2 Carbon at the Sulfur Synthesis of (Hetero)Arylthiatriazines.

Substituents bound to the sulfur *via* a sp^2-hybridized carbon atom may also be introduced. The same approach as for 1-alkylthiatriazines can be applied for the preparation of 1-aryl- and 1-heteroarylthiatriazines (Scheme 15).

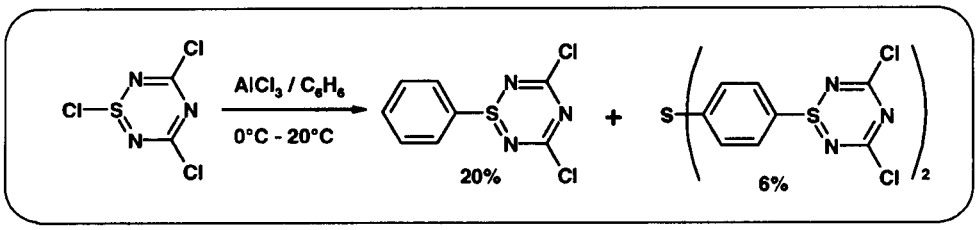
Scheme 15



The corresponding aryl- or heteroaryl-metal derivatives have first to be generated. They are obtained either by proton abstraction with a strong base like an alkyllithium or from the corresponding halide through metal-halogen exchange reaction or direct reaction with a metal like magnesium or lithium. The following step consists of a transmetallation reaction using zinc chloride or aluminium chloride and subsequent treatment with trichlorothiatriazine. The desired compounds are usually obtained in very high yields.

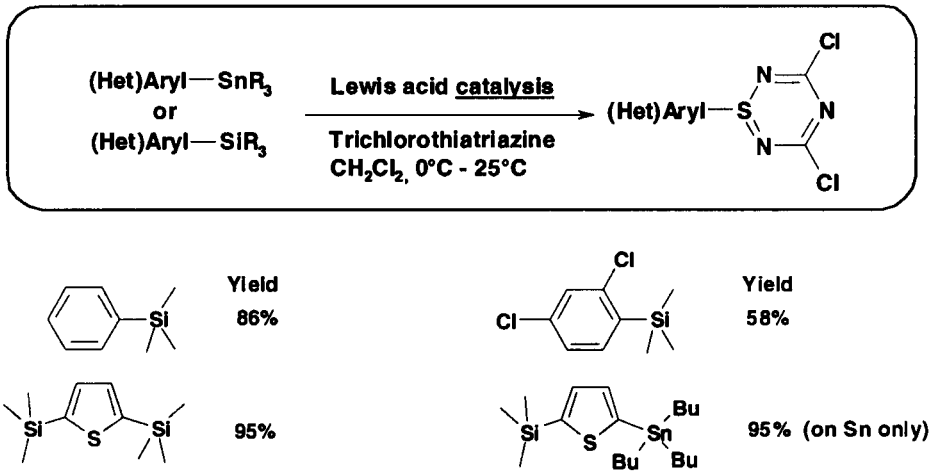
Arylation at the sulfur of thiatriazines can also be obtained when using Friedel-Crafts reaction conditions, but this method is not always useful for preparative purposes as can be seen in the example with benzene (Scheme 16).

Scheme 16



A much more efficient reaction for replacing the sulfur chlorine by an aromatic or heteroaromatic cycle is the *ipso*-thia-desilylation or the *ipso*-thia-destannylation. In these reactions, the aromatic moiety is fitted with a trialkylsilyl or a trialkylstannyl group, which activate the *ipso*-position toward electrophilic substitution. Lewis acid catalysis is required, but the reaction conditions are very mild and the yields are usually very high (Scheme 17). It is important to notice that the position bearing the tin derivative is much more activated than the one with silicon.

Scheme 17



These compounds are usually not commercially available and must be synthesized first, most often through metallation by a classical way followed by silylation or stannylation. This sequence may seem longer than directly treating the organometallic derivative with zinc chloride followed by trichlorothiatriazine, but in some cases it is a real advantage, especially if the metallation is not regiospecific and the isomeric silylated or stannylated products can be separated or if the anion is not stable enough at the temperature required for the transmetallation with zinc chloride.

Synthesis of 1-α-Alkenylthiatriazines.

Use of Alkenyl-metal Derivatives.

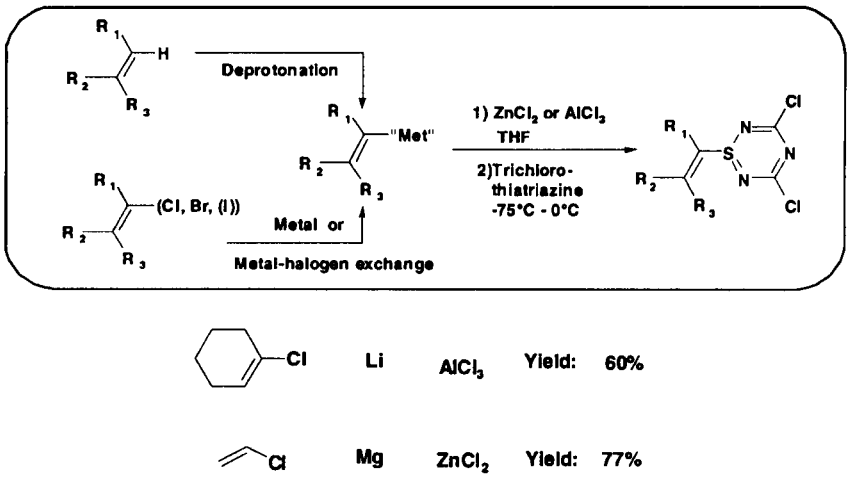
The introduction of α-alkenyl substituents at the sulfur of thiatriazine can be obtained in a similar way as for the aryl or heteroaryl cases. Alkenyllithium or alkenylmagnesium halide has to be treated with zinc chloride or aluminium chloride prior to the reaction with trichlorothiatriazine at low temperature (Scheme 18).

The starting alkenylmetal derivatives may be obtained from an activated alkene by deprotonation with a strong base or from the corresponding alkenyl halide by metal-halogen exchange or by direct reaction with a metal.

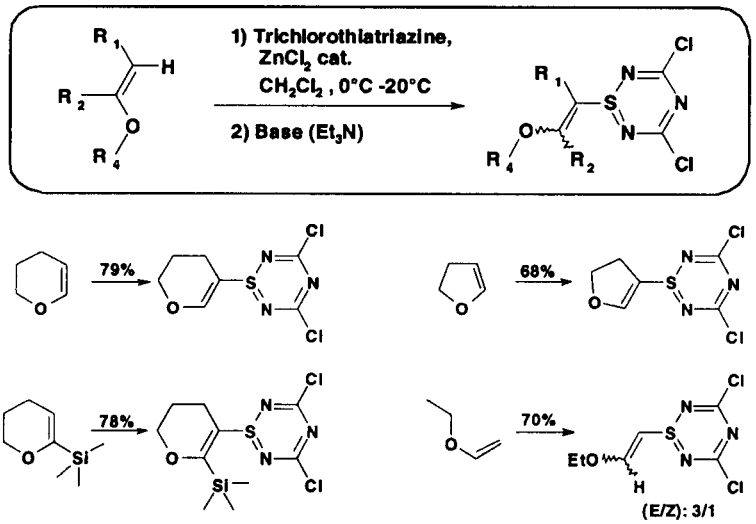
Reaction with Enol Ethers.

Some electron rich olefins, like enol ethers react directly with trichlorothiatriazine under very mild conditions. The reaction is Lewis acid catalyzed (Scheme 19).

Scheme 18



Scheme 19



The first product of the reaction results from the addition of the S-Cl bond to the olefin, the sulfur atom being attached to the carbon in β-position to the oxygen and the chlorine atom at the α-position. Hydrogen chloride can be easily eliminated under mild alkaline conditions to regenerate a double bond if the β-carbon carries a hydrogen atom. The reaction works with cyclic and acyclic enol-ethers. In the latter case, *E*:*Z* mixtures of products are obtained.

Use of Alkenylzirconocenes.

Alkenylzirconocene derivatives can also be used to introduce an alkenyl group at the sulfur of the thiatriazine system. Terminal alkynes are usual starting materials for this approach.

In one variation, a terminal alkyne is treated with Schwartz' reagent to generate an (*E*)-alkenylzirconocene derivative, which reacts with trichlorothiatriazine at a low

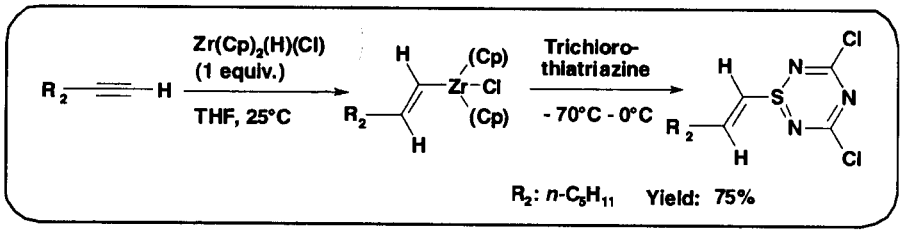
temperature (Scheme 20). The reaction is stereospecific. No trace of the (Z)-derivative could be detected.

In another variation, the terminal alkyne is treated with trimethylaluminium and zirconocene dichloride to form a β-methylated-α-alkenyl zirconocene derivative [13]. The transfer of the organic group is performed with high yields (Scheme 21). This sequence is stereo- and regio-specific. The methyl substituent is in β-position and *cis* to the sulfur.

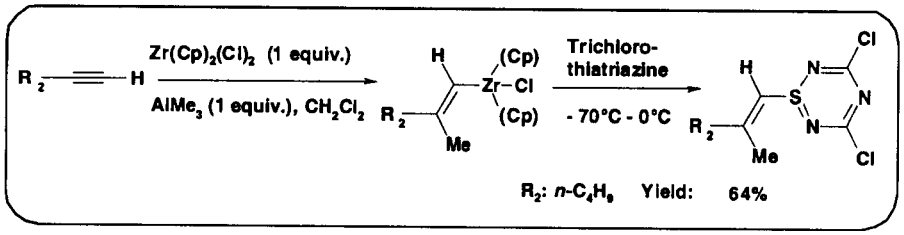
C. Introduction of sp Carbon at the Sulfur: Reaction with Alkynylalanates.

The introduction of α-alkynyl substituent at the sulfur is also possible by using lithium tetraalkynylalanates (Scheme 22). The preparation of these reagents starting from terminal alkynes and lithium aluminium hydride has been reported in the literature [14]. They react with trichlorothiatriazine at low temperature. Two alkynyl groups are transfered in moderate to good yields.

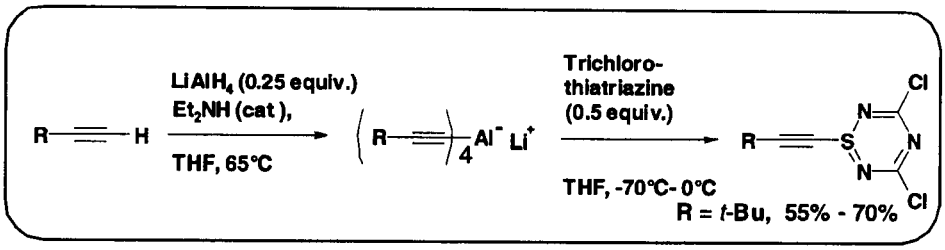
Scheme 20



Scheme 21



Scheme 22



It has been shown that it is possible to introduce a large variety of substituents at the sulfur of thiatriazine with the carbon atom bound to the sulfur being of any state of hybridization.

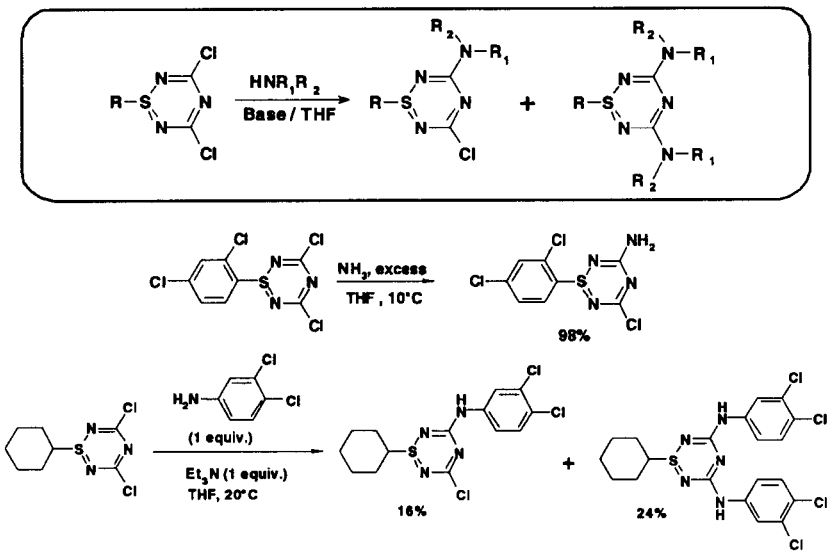
The 1-organyldichlorothiatriazines obtained this way can now be subjected to further substitution reactions on the 3- and 5-positions.

4. Substitution at the 3- and 5-Positions.

A. Reaction of 1-Carbo-3,5-dichloro-1λ^4-1,2,4,6-thiatriazines with Amines.

When 3,5-dichlorothiatriazines are treated with a primary or a secondary amine, both chlorine atoms may be substituted (Scheme 23). The introduction of a first amino group on the heterocycle deactivates the last position. If the amine used is nucleophilic enough, the last substitution can proceed, otherwise the reaction stops at the monosubstituted stage. It is not unusual that a mixture of mono- and diamino derivatives together with starting material is obtained if no excess of amine is used.

Scheme 23



On the contrary, if a dichlorothiatriazine is subjected to an excess of dry ammonia, only the monoamino derivative is obtained in very good yield.

B. Reaction of 1-Carbo-3,5-dichloro-1λ^4-1,2,4,6-thiatriazines with Alcohols and Phenols.

Alcohols and phenols react with 3,5-dichlorothiatriazines in the presence of a base (Scheme 24). Both chlorine atoms may be substituted, so that the reaction often results in a mixture of compounds. The introduction of a first oxy group does not deactivate the last position The preparation of monosubstituted products in good yields requires a careful control of the reaction conditions, but purification is usually necessary.

C. Synthesis of 3-Amino-5-aryloxy-1-carbo-1λ^4-1,2,4,6-thiatriazines.

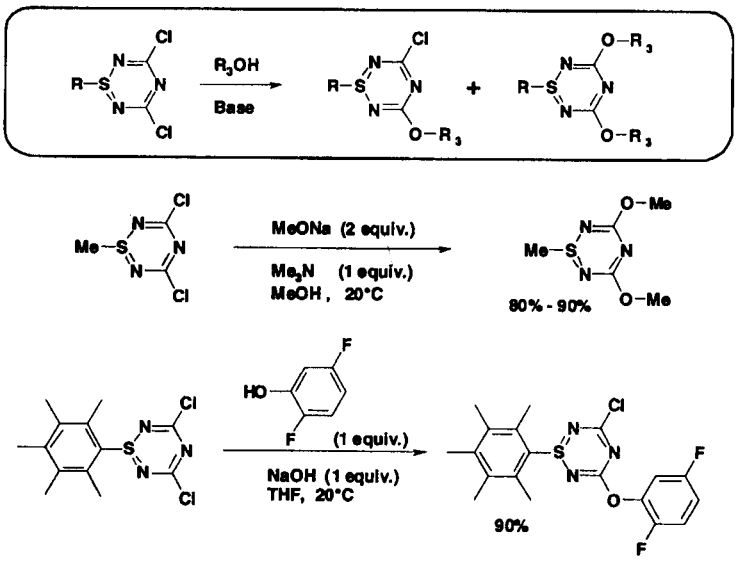
Thiatriazines bearing an amino group and a phenoxy group can be prepared starting either from the amino-chloro derivative or the aryloxy- chloro derivative (Scheme 25).

In the first case, the chlorine atom to be substituted is deactivated by the amino group. Trimethylamine can be used to reactivate this position. This leads first to the introduction of the trimethylammonium moiety at the heterocycle, which can be easily displaced by the phenolate. The yields obtained by this method are high (typically over 90%) and the reaction may be performed in a two-phase system (water/organic solvent) where aqueous sodium hydroxide, aqueous trimethylamine and the phenol can be introduced all at once.

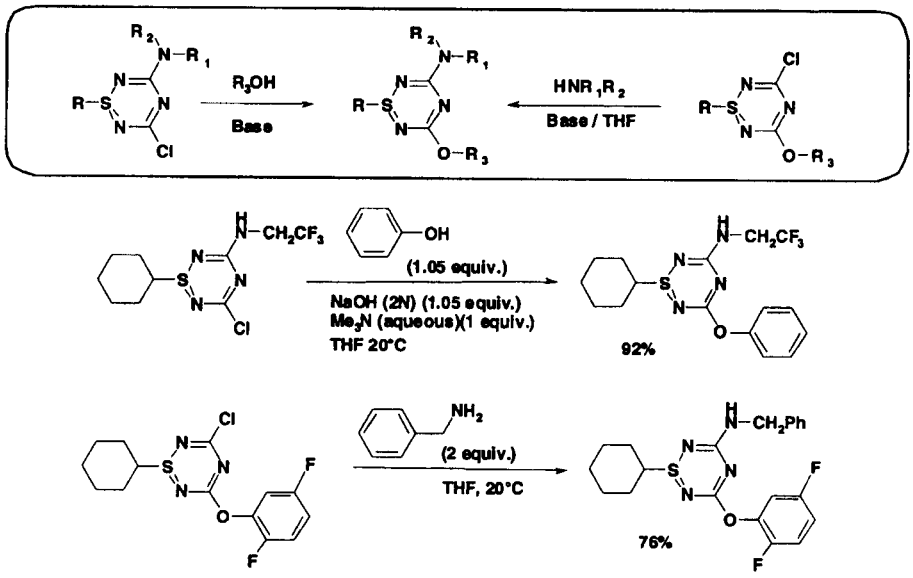
In the case of amination of the chloro-phenoxythiatriazines, further activation is not needed. Depending on the phenoxy group already present on the heterocycle, a side reaction where the phenolate is the leaving group may be observed.

If the target molecule bears an unsubstituted amino group, the easiest way is to treat first the dichlorothiatriazine with excess of ammonia in an organic solvent to yield selectively the amino-chloroderivative, which is then submitted to the reaction with the phenolate in the presence of trimethylamine.

Scheme 24



Scheme 25



5. Structural and Stereochemical Aspects of $1\lambda^4$-1,2,4,6-thiatriazines.

X-Ray structure determination of $1\lambda^4$-1,2,4,6-thiatriazines show that the heterocyclic system is not planar (Figure 2). The sulfur atom points out of the average plane of the five other atoms. The two S-N bonds are almost same length. The configuration around the tetragonal sulfur is noteworthy. The substituent points out of the average plane, making with it almost a right angle.

If the 3- and 5-positions are differently substituted, the sulfur atom becomes an asymmetric center. Introduction of an asymmetric substituent leads to diastereoisomers.

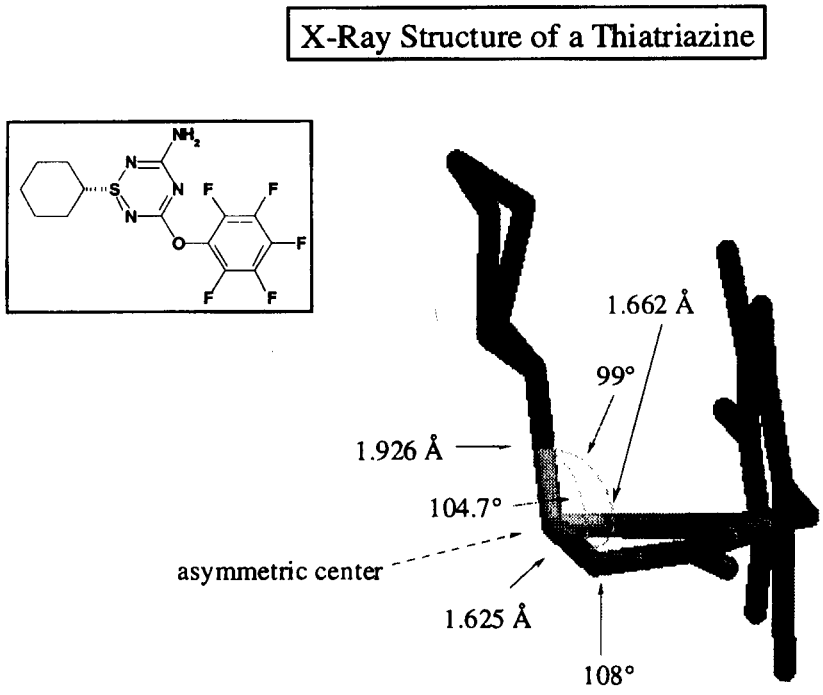


Figure 2.

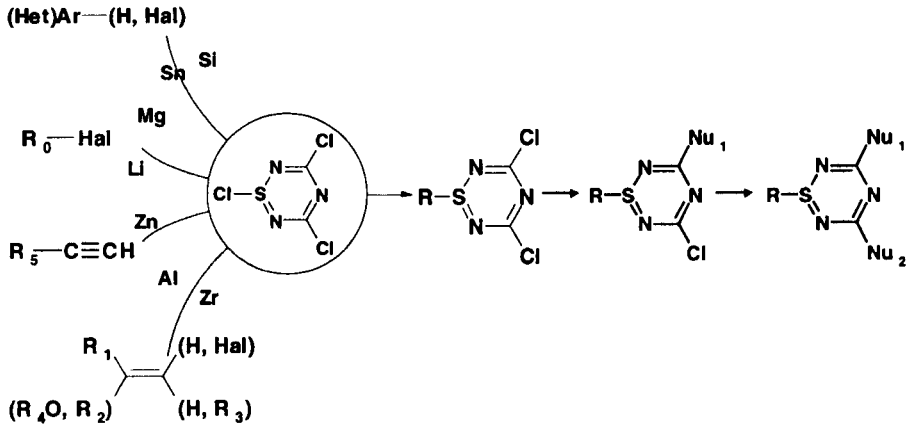
The configuration at the sulfur atom is very stable. No racemization was observed on enantiomerically pure compounds under a whole range of conditions.

In cases where enantiomers of herbicidally active thiatriazines were separated, the biological activity was found in one enantiomer only.

Conclusions.

A novel strategy has been developed for the synthesis of 1-carbo-1λ⁴-1,2,4,6-thiatriazines. Very few of these compounds were described in the literature. They now can be obtained from easily available 1,3,5-trichloro-1λ⁴-1,2,4,6-thiatriazine. The short and convergent synthesis consists of first replacing the chlorine atom at the sulfur of this central building block with a carbon-based group, then stepwise substituing the two other chlorine atoms by adequate nucleophiles (Scheme 26) [15]. Different methodologies have been made available to introduce the carbon-based substituent at the sulfur of the heterocycle. Any hybridization state of this carbon is accessible. Most

Scheme 26
Synthesis of 1l4-1,2,4,6-Thiaatriazines



methods rely on organometallic chemistry. A large variety of starting materials can be used.

The substituent at the sulfur points away from the average plane of the heterocycle. If the 3- and 5-positions are differently substituted the sulfur atom is an asymmetric center. When the enantiomers of herbicidally active thiatriazines were separated, only one showed biological activity and no racemization could be observed.

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