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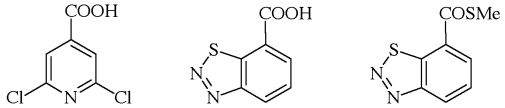
Introduction.

To our knowledge, there is no immune system equivalent to that of mammals existent in plants. Nevertheless, when plants have been treated locally with pathogens 100 years ago a response very similar to the immune reaction was observed. A few days after such a local treatment the plant develops resistance against a new infection *via* a mechanism which up to now is not very clear. But in contrast to the very specific immunization initiated by vaccination of animals or man the treated plant shows a broad-spectrum resistance against a variety of different pathogens. This "induced resistance" is effective mostly for weeks or months and extended to all parts of the affected plant, also those grown later. It is clearly a systemic property, therefore it is called "systemic acquired" or "systemic activated resistance" (SAR) [1]. Unfortunately, it turned out that such biologically induced resistance is not applicable efficiently under field conditions so that this promising concept has not been established in plant protection for a long time. Many years later the observation was made that the phenomenon of SAR can be triggered also by small amounts of selected organic compounds which themselves, including their metabolites, show no *in vitro* activity against the applied pathogen. In the late 80's this important discovery led finally to first successful attempts to develop commercial products with SAR-activity. Bioactive compounds which are able to induce "systemic acquired resistance" nowadays are called "resistance inducers" or "plant activators".

First development products with pronounced SAR-activity were found by Ciba researchers within derivatives of 2,6-dichloroisonicotinic acid. As in many similar cases, a new lead structure was later discovered just by serendipity and 1,2,3-benzothiadiazole-7-carboxylic acid became the starting point for the development of the first commercial product. In 1996 its methylthioester *acibenzolar-S-methyl* was introduced under the trade name Bion® [2]. Initially applied against powdery mildew on wheat, in the meantime it shows promising activity in many other crops as well (Scheme1).

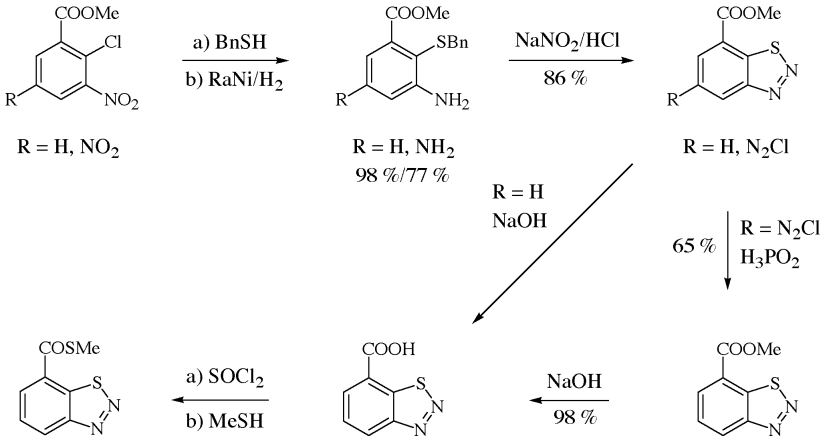
Scheme 1



CGA 41396 ***Acibenzolar-S-methyl*** **(Bion)**

The strategy developed for the synthesis of the Bion-type benzothiadiazoles in the laboratories of Ciba resp. Novartis CP is depicted in Scheme 2. Starting with esterification of commercially available 2-chloro-3-nitrobenzoic acid the *S*-functionality was introduced by nucleophilic substitution of the chlorine with benzylthiol and hydrogenation of the nitro group afforded the amino compound. Cyclization *via* intramolecular coupling reaction of the diazonium salt to

Scheme 2

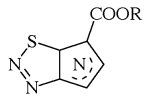


the sulfur and subsequent loss of benzyl chloride led to the corresponding benzo[1,2,3]thiadiazole-7-carboxylic acid which was transformed to Bion® *via* the acid chloride. The yields of the single steps are excellent, the reagents cheap, but the starting product is quite expensive for an industrial production. Later a substantial improvement was achieved by starting with the cheap dinitro compound and after the cyclization, the remaining diazonium group was reduced by hypophosphorous acid in an one-pot reaction (Scheme 2).

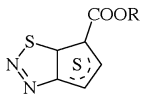
Evaluation of biological results of a large series of derivatives and structural modifications gave insights into structure-activity-relationships. Most derivatives of the carboxylic acid like esters, thiolesters, thionoesters, dithioesters, carboxamides, thioamides, hydrazides, and the nitrile show good inducing activity. The activity dropped significantly with the vinylogous acid, the corresponding aldehyde and its derivatives, the alcohol and related ethers. It was totally lost with the homologous acid, the sulfonic acid, the sulfonamide, the phosphinic acid, the nitro and the methyl compound. The position of the carboxylic acid, adjacent to the sulfur atom of the thiadiazole, seems to be crucial for the SAR-activity and loss of bioactivity was mostly observed when substituents were introduced into the benzo-moiety. Replacement of the 1,2,3-thiadiazole ring by various other heterocyclic ring systems led mainly to products of decreased or no bioactivity.

Being interested in new compounds with improved bioactivity, we extended our efforts later to heterocyclic systems where the benzo-part was modified and in this summary the results achieved within the synthetic project directed towards various isomers of [1,2,3]thiadiazolopyridines [3], thieno[1,2,3]thiadiazoles [4] and pyrrolo-[1,2,3]thiadiazoles [5] are presented (Scheme 3).

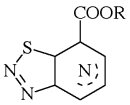
Scheme 3



Pyrrolo[1,2,3]thiadiazoles



Thieno[1,2,3]thiadiazoles



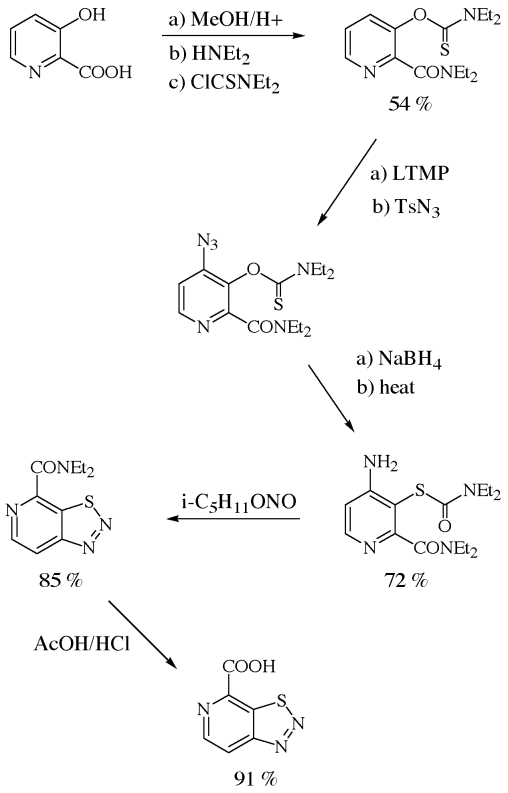
[1,2,3]Thiadiazolopyridines

[1,2,3]Thiadiazolopyridinecarboxylic Acids.

The general strategy was to start from commercially available mono- or disubstituted pyridine derivatives, to introduce the missing substituents *via* directed lithiation and to accomplish the cyclization using the diazotization strategy applied successfully for Bion®.

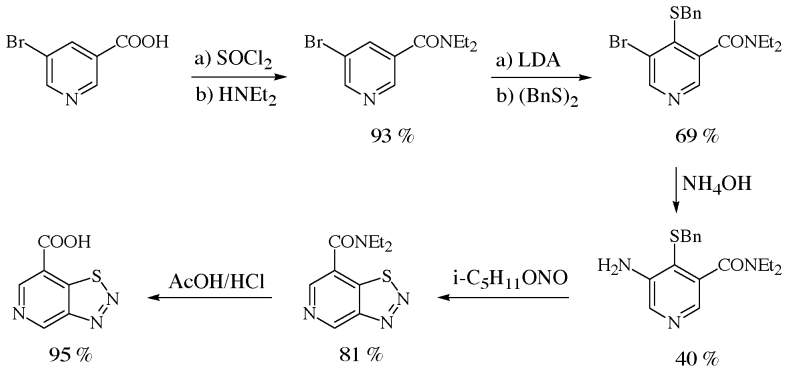
In the first series 3-hydroxypicolinic acid was transformed to the diethylamide *via* the methyl ester followed by formation of the *ortho*-directing group by attachment of the *N*,*N*-diethylthiocarbamoyl moiety to the hydroxy group. Subsequently, the amino group was introduced at the 4-position by directed lithiation, quenching with tosyl azide and reduction of the azide intermediate with sodium borohydride. Kwart-Newman rearrangement led to an *ipso*-exchange of the oxygen and the sulfur leading to the thiolcarbamate which was cyclized by using the standard ring closure procedure *via* diazotization. The desired [1,2,3]thiadiazolo[5,4-*c*]pyridine-7-carboxylic acid was finally available by acidic hydrolysis of the carboxamide (Scheme 4).

Scheme 4

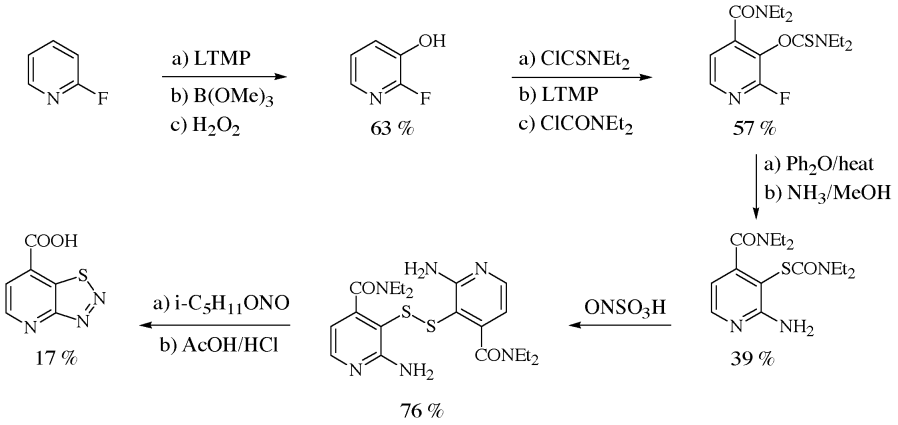


The synthesis of the [1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxylic acid started from 5-bromonicotinic acid. The corresponding diethylamide, available *via* the acid chloride, was lithiated at the 4-position with LDA and the *S*-functionality introduced by quenching with dibenzyldisulfide. Subsequent displacement of the bromine in the 5-position by reaction with ammonia gave a moderate yield of the amine but the cyclization and subsequent hydrolysis to the target compound was again very successful. (Scheme 5)

Scheme 5



Scheme 6

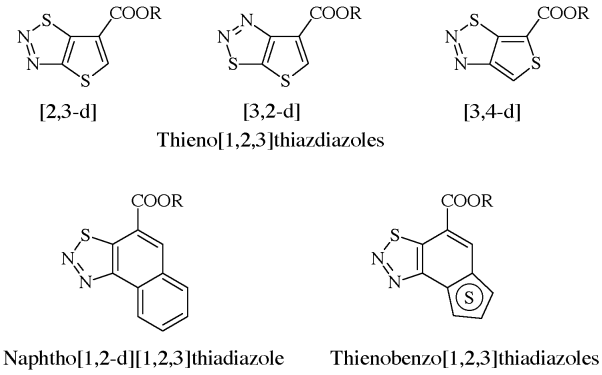


2-Fluoropyridine was the precursor for the third isomer. Lithiation adjacent to the fluorine using lithium 2,2,6,6-tetramethylpiperidide and quenching with trimethylborate yielded the boronic acid which in turn was oxidized to afford 2-fluoro-3-hydroxypyridine. Again the directing group was placed on the hydroxy group followed by introduction of the carboxamide to the 4-position *via* lithiation and quenching with *N*,*N*-diethylcarbamoyl chloride. Kwart-Newman rearrangement and nucleophilic substitution of the fluorine with ammonia again produced a substitution pattern useful for cyclization. The yield of 17% in the last step leading to the [1,2,3]thiadiazolo-[4,5-*b*]pyridine-7-carboxylic acid was a bit disappointing in comparison to the other two series (Scheme 6).

Thieno[1,2,3]thiadiazoles.

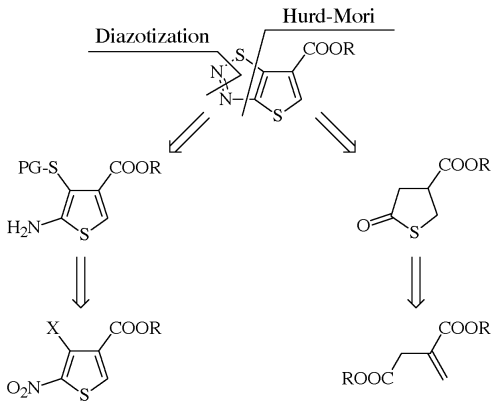
Keeping in mind the structure-activity relations established in the benzothiadiazole series, the thieno[2,3-*d*][1,2,3]thiadiazole system was the one of major interest, so the emphasis was on this system, but the elaborated and optimized synthetic sequences were useful for other bicyclic isomers as well and they allowed also the construction of corresponding tricyclic systems [6] shown on the bottom of Scheme 7.

Scheme 7



Two major strategies were taken into account for the construction of the desired thieno[2,3-*d*][1,2,3]thiadiazole-6-carboxylic acid derivatives. For the cyclization *via* an intramolecular coupling reaction similar to that applied in the benzo- and pyrido-series, we required 5-nitrothiophene-3-carboxylates bearing a good leaving group X in the 4-position. The second approach was based on the Hurd-Mori cyclization commonly applied to ketones. We extended the utilization of this reaction to the thiolactone leading back to itaconic acid (Scheme 8).

Scheme 8

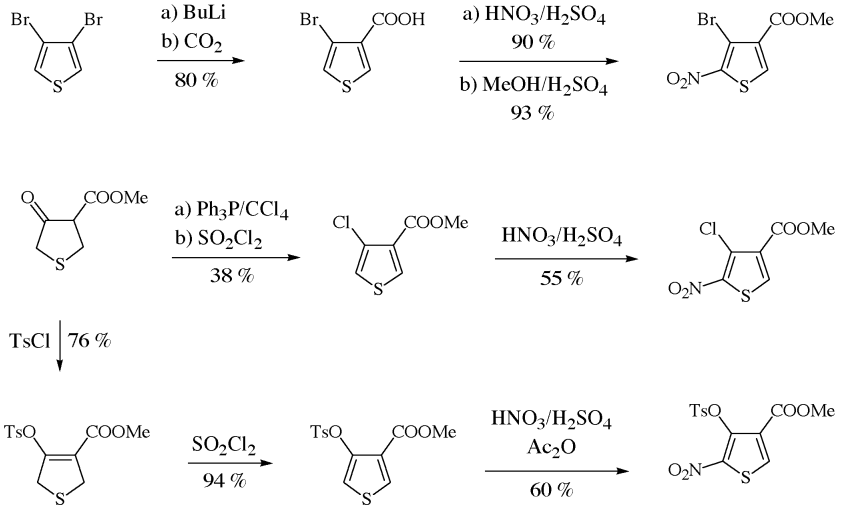


In the first approach, we started with 3,4-dibromothiophene. Bromine-lithium exchange with *n*-butyllithium at -80 °C and quenching with carbon dioxide was followed by trivial steps where the bromo acid was nitrated in the 5-position and the resulting nitro acid esterified. Although this approach was published already in the literature [7] major changes were necessary for yield improvement and especially for scale-up. In alternative sequences the desired substitution pattern with other leaving groups X was available starting with 4-thiophanone-3-carboxylate. Reaction with triphenylphosphine/tetrachloromethane afforded the 4-chloro-2,5-dihydro-3-thiophenecarboxylate in moderate yields, or the ketoester was *O*-tosylated. In each case, aromatization was achieved with sulfuryl chloride according to a method published by Rossy *et al.* [8]. Both products were nitrated, in the case of the tosyloxy-compound under anhydrous conditions, leading to useful intermediates (Scheme 9).

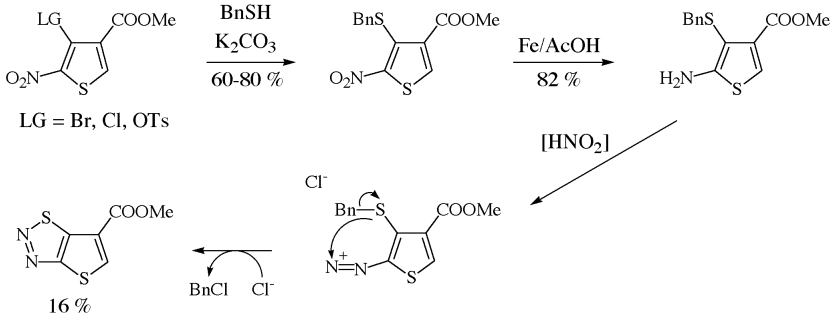
The *S*-functionality was introduced generally by nucleophilic substitution of the corresponding leaving group with benzylthiolate. Reduction of the nitro group with iron and acetic acid yielded the amino ester, which like most amino thiophenes, was quite unstable but sufficiently pure to be used directly in the cyclization step. Diazotization and subsequent cyclization finally afforded the expected product, which upon laborious separation and purification steps, was obtained in a disappointing 16% yield. Although we tried very hard, unfortunately, we were not able to improve the yield of this final step (Scheme 10).

It is known from literature that diazotizations of aminothiophenes are successful only in cases where no free positions in the electron-rich system are available. These activated positions can be attacked either by the nitrosonium ion or by the intermediate diazonium ion in a diazo-coupling reaction. Similar problems were reported by Sauter and Deinhammer [9] some time ago when they tried the synthesis of thienotriazinones and they actually isolated a corresponding 5-nitroso compound. To prove if this fact can be the reason for the low yield, in the present case we synthesized the corresponding 5-methyl compound using one of the approaches developed in the course of the synthesis of the unsubstituted ester. A yield

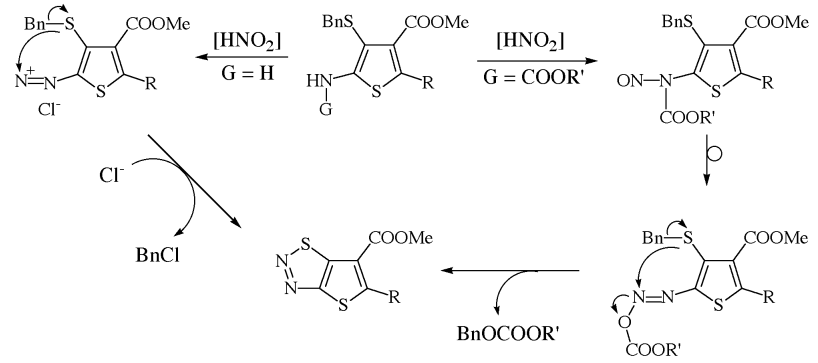
Scheme 9



Scheme 10



Scheme 11

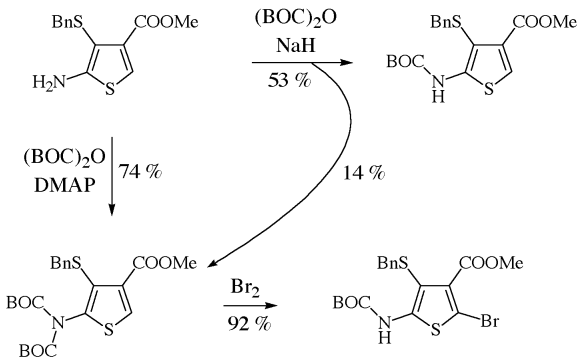


improvement to 55% in the cyclization step confirmed our opinion but, unfortunately, introduction of the methyl group led to loss of bioactivity.

In a series of papers which appeared in the late 50's, Huisgen *et al.* [10] and later White [11] published results of an interesting reaction where acyl groups of *N*-nitroso carboxanilides were rearranged by a N-O-migration to acyloxy diazo-compounds. Although the main interest of both groups was directed towards reactions where molecular nitrogen was lost, they mentioned also a few results where the acyloxy group was simply replaced by nucleophiles. This observation prompted us to try to solve our problems and to improve the yield of the thiadiazole annelation by modifying the reaction mechanism. As depicted in Scheme 11, rearrangement of an appropriate *N*-nitrosocarbamate should be followed by an intramolecular attack of the adjacent *S*-functionality leading to the desired thieno[1,2,3]thiadiazole without appearance of a diazonium salt. Due to the decreased electron donating ability of the acylated amino group, nitrosation of the thiophene ring should also not be prevalent in this case. Fortunately, this idea could be verified by using BOC-protected aminothiophenes (Scheme 11).

Attempts to place the *tert*-butoxycarbonyl group on the amino group using sodium hydride as a base unfortunately led to partial introduction of a second *tert*-butoxycarbonyl group. Later we observed that the bis-acylated compound, available in good yield by using 2 equivalents of di-*tert*-butylpyrrocarbonate and 4-dimethylaminopyridine, was even a better substrate in the desired cyclization reaction.

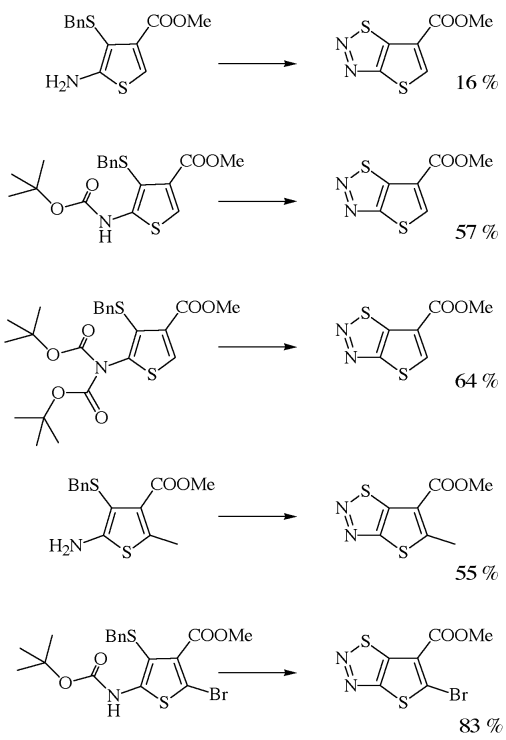
Scheme 12



Under strong acidic conditions of the nitrosation reaction, one of the *tert*-butoxycarbonyl groups was cleaved, releasing the NH-functionality for the following nitrosation. The same cleavage was observed under the conditions of the bromination yielding the 2-bromo product which was also cyclized (Scheme 12).

Scheme 13 shows the summary of the results of both cyclization strategies. It can be considered that in all cases, unsubstituted and substituted ones, the yields are improved significantly when using the new cyclization methodology.

Scheme 13

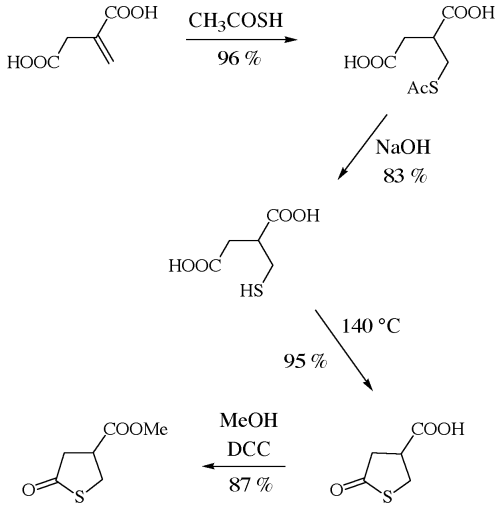


Not being really satisfied with the overall yield of the discussed sequence, we tried a second approach *via* the Hurd-Mori cyclization, a versatile reaction known for 45 years and very useful for the annelation of a 1,2,3-thiadiazole ring [12]. This can generally be achieved by reacting hydrazones of cyclic or acylic ketones bearing appropriate acyl leaving groups (*e.g.*, tosyl, alkoxycarbonyl or carbamoyl) with sulfur dichloride or thionyl chloride.

As mentioned previously, we had to adopt this reaction for the synthesis of our target compound. Instead of using a ketone, we started from a thiolactone as shown in Scheme 14. We have been encouraged to run this experiment by a paper of Lee *et al.* [13] who already tried Hurd-Mori cyclizations with some open-chain dithioesters.

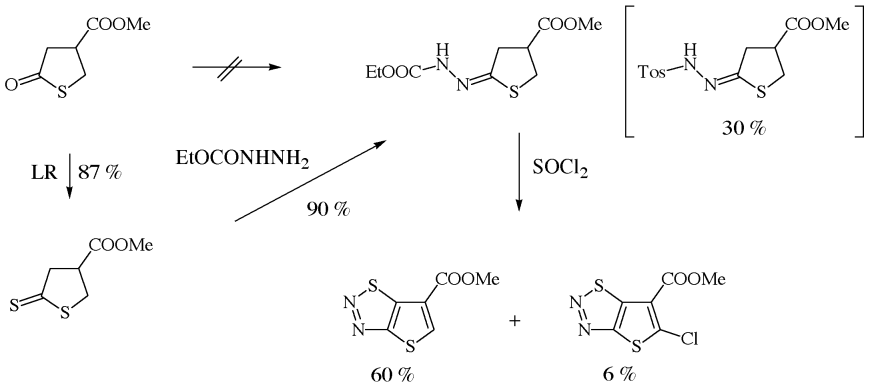
Some older literature [14] was available for the synthesis of precursors of this thiolactone but the procedures were improved methodically and the yields optimized. The sequence started with nucleophilic addition of thioacetic acid to itaconic acid followed by *S*-deprotection by alkaline hydrolysis and thermal cyclization to the 5-thiophanone-3-carboxylic acid. For the esterification in the last step, we had to use the dicyclohexyl carbodiimide method, as under acid-catalyzed conditions, partial cleavage of the thiolactone and formation of the mercapto diester was observed (Scheme 14).

Scheme 14



As no reaction was observed with the thiolactone, it was converted with Lawesson´s reagent to the more reactive dithiolactone. In contrast to only 30% yield of the reaction with tosylhydrazine, the dithiolactone reacted smoothly with ethyl carbazate. In the following Hurd-Mori reaction, the carbazate derivative gave again higher yields as the tosylhydrazone. This is noteworthy in so far, as the tosyl group is usually the preferred leaving group when cyclic ketones are used. It is important to emphasize that in all our attempts to perform the Hurd-Mori cyclization none of the expected 2,3-dihydro product was detected, but two aromatized products were isolated instead, the target compound as the major product acompanied by 6% of a product bearing a chlorine in 5-position. As these products were not easily separable, we were lucky as we found a way to prevent the formation of this chlorinated by-product simply by using more vigorous reaction conditions, 80 °C instead of 25 °C, so the target compound was obtainable in 66% yield (Scheme 15). By this optimized procedure, an over-all yield of 35% was achieved in a 7-step-sequence which is suitable now for the preparation of large amounts of the target compound starting from cheap itaconic acid, using cheap reagents

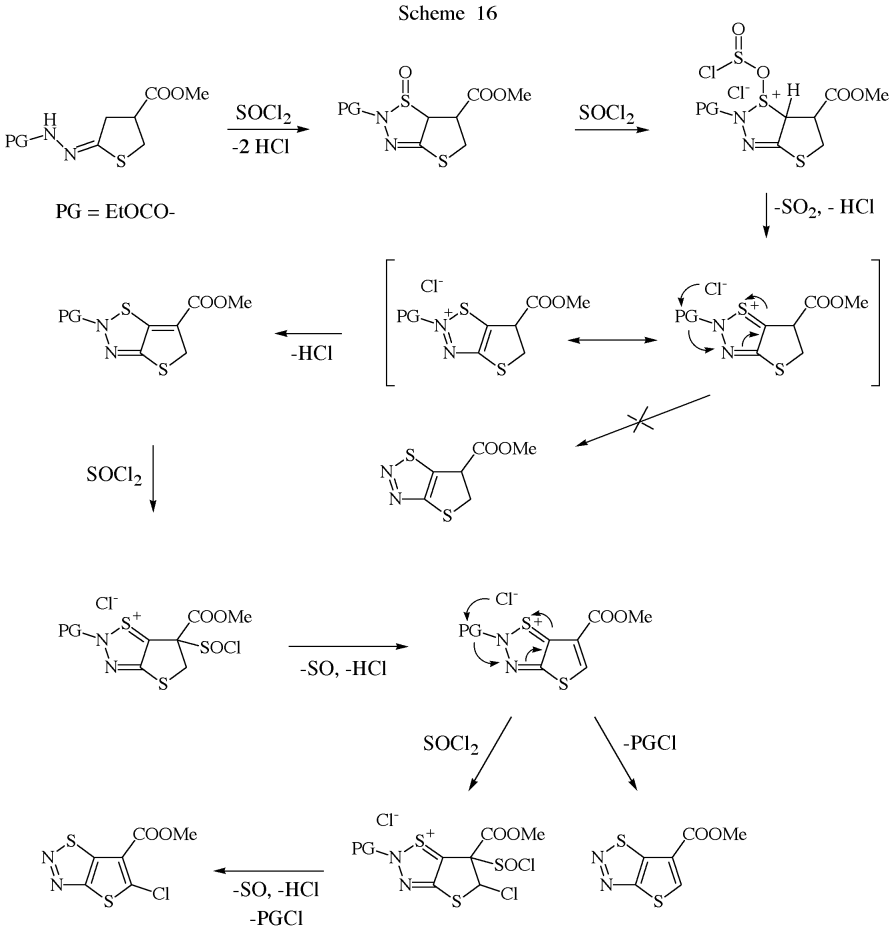
Scheme 15



and easily applicable reaction conditions. This sequence allowed now direct access to a large series of various derivatives necessary for biological testing and structure-activity-relation studies.

Although the mechanism of the Hurd-Mori reaction is still a matter of speculation, the following mechanistic suggestions may be plausible. In the first step thionyl chloride is bridging the nucleophilic carbon of the enehydrazine tautomer and the nitrogen bearing the leaving group. Then another thionyl chloride can react with the oxygen, and in a Pummerer-like rearrangement a sulfonium intermediate is generated. Elimination of the leaving group, in the present case as ethyl chloroformate or ethyl chloride and carbon dioxide, respectively, should yield the expected

Scheme 16

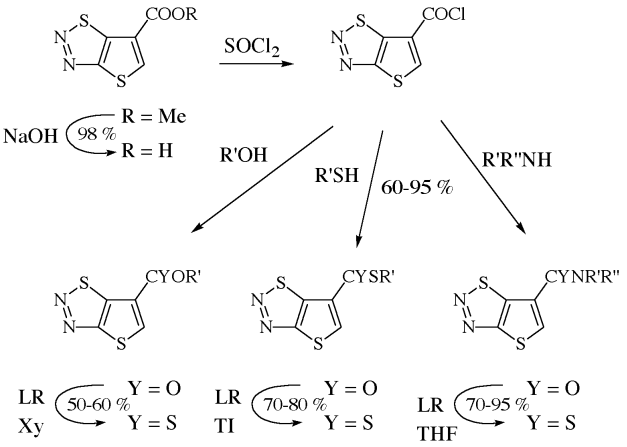


2,3-dihydro compound which in no case was detectable. We assume that immediate HCl-elimination takes place instead, forming an electronically favoured, conjugated push-pull substituted double bond as depicted in Scheme 16.

This double bond adds thionyl chloride again followed by an elimination to form the 2,3-double bond. Now the cleavage of the leaving group can take place yielding the target compound. The formation of the chlorinated by-product can be explained by thionyl chloride addition to the intermediate with the new 2,3-double bond, which is again push-pull substituted. After elimination of SO and HCl, the intermediate is losing the leaving group yielding finally the 5-chloro compound. As mentioned previously, the formation of this by-product can be prevented simply by raising the temperature from room temperature to 80 °C, thus enhancing the elimination of the leaving group and preventing addition of another equivalent of thionyl chloride. Results obtained with similar substrates later, let us to assume that an electron withdrawing group in the β-position to the S-atom, originating from thionyl chloride, increases the tendency of the system to aromatize.

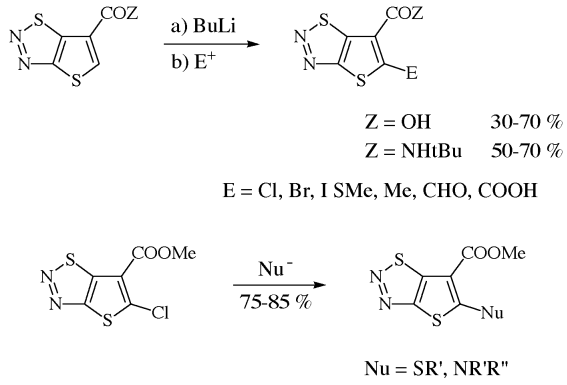
The following two schemes show the extensive variations of the target molecule undertaken to get enough biological data for a structure-activity analysis. Starting from the acid chloride, available from the methyl ester by alkaline hydrolysis and reaction of the carboxylic acid with thionyl chloride, a series of various esters, thioesters and carboxamides were available leading to corresponding thionoesters, dithioesters and thioamides with Lawessons reagent. The nitrile, the aldehyde and its derivatives were all obtained using routine chemistry (Scheme 17).

Scheme 17



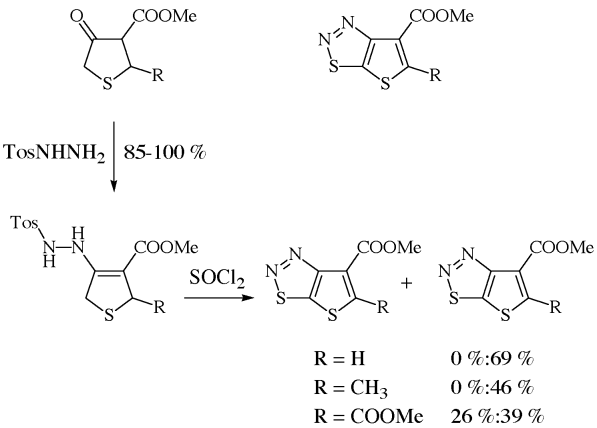
Various substituents were introduced into the 5-position *via* directed lithiation of the carboxylic acid or with even better results using the *N-tert*-butylcarboxamide. The 5-chloro compound, the by-product of the original Hurd-Mori cyclization, was now available in excellent yields by lithiation and quenching with hexachloroethane. Introduction of several other substituents was enabled *via* nucleophilic displacement of the activated chlorine [15] (Scheme 18).

Scheme 18



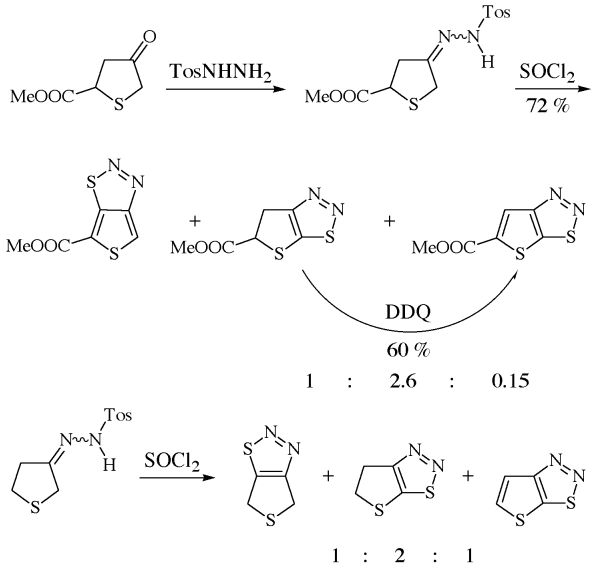
In the course of our project, we used the Hurd-Mori reaction also for the construction of isomeric thieno[1,2,3]thiadiazole systems and it was interesting to compare the results with those from the [2,3-*d*]-series. Three 4-thiophanone-3-carboxylates depicted in Scheme 19 were converted to the tosylhydrazones, which according to NMR-spectroscopy, are exclusively present as tautomeric enehydrazines. As expected, the subsequent Hurd-Mori reaction yielded the isomeric thieno[3,2-*d*]-[1,2,3]thiadiazole system but in the latter case the aromatization was not completed and dehydrogenation of the mixture with 2,3-dichloro-5,6-dicyanobenzoquinone led finally to the aromatic diester.

Scheme 19



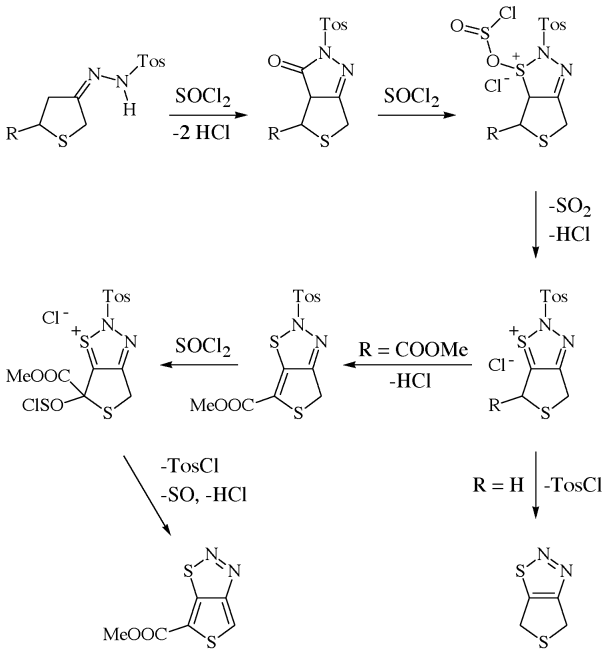
In contrast to these results, the Hurd-Mori reaction of 4-thiophanone-2-carboxylate led mainly to the dihydro [3,2-*d*]annelated product accompanied only by small amounts of aromatization product (Scheme 20). As there is no possibility to build a push-pull system in this case, the tendency for aromatization is not that high. Although preference for the *b*-annelation can be considered, also some [3,4-*c*]-annelation product, again fully aromatized, was detected. After separation from the [3,4-*c*]-isomer, the resulting mixture of the [3,2-*d*]-products was dehydrogenated again with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. It is interesting to compare these results with those obtained with 3-thiophanone itself. It can be observed that the ratio of the *b*-annelated and the *c*-annelated product did not change when the ester functionality in the 5-position is missing, but the aromatization is strongly supported by the ester group in the case of the *c*-annelated product. On the other hand, a decreased tendency for the aromatization can again be observed in the case of the *b*-annelated product bearing the ester group in the 5-position.

Scheme 20



An explanation for the first observation is given in Scheme 21, but we have no explanation for the fact that an ester group in the 2-position lowers the aromatization tendency. Looking at the final steps of the proposed mechanism, it is evident that in the case of 3-thiophanone (R = H) there is no possibility of setting up a push-pull substituted double bond, which to our opinion, is promoting the elimination of hydrochloric acid, addition of thionyl chloride followed by subsequent aromatization. In the case of 4-thiophanone-2-carboxylate (R = COOMe), such a double bond can be formed by elimination of hydrochloric acid leading now exclusively to aromatization, as it was observed.

Scheme 21

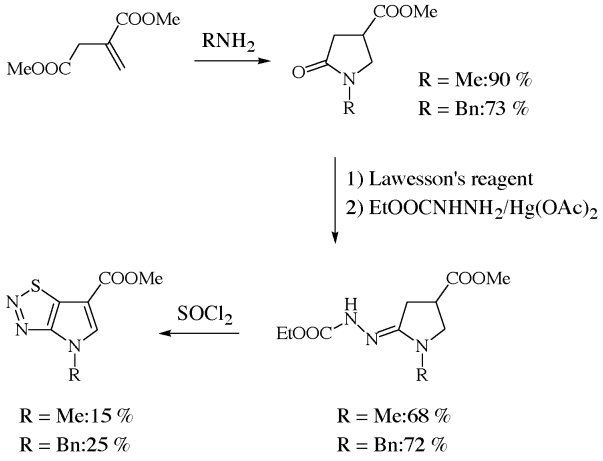


Pyrrolo[2,3-*d*][1,2,3]thiadiazoles.

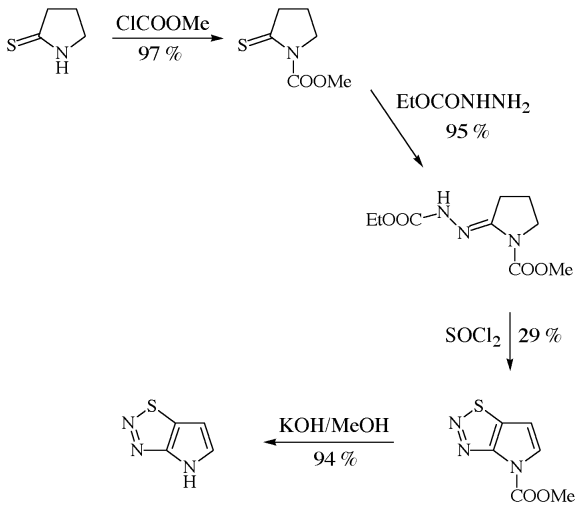
Having been successful by using the Hurd-Mori reaction for the synthesis of all isomeric thieno[1,2,3]thiadiazoles, we had also in mind to adopt this methodology for the synthesis of this new ring system. According to the literature up to now, thioamides have never been used for this cyclization methodology. To get an appropriate substrate, itaconic acid was reacted with benzylamine or methylamine, respectively, followed by esterification to obtain the corresponding *N*-alkyl-5-pyrrolidinone-3-carboxylates. It must be emphasized that condensation of the thiolactam with ethyl carbazate was achieved only when the evolving hydrogen sulfide was quenched with mercuric acetate. Although the Hurd-Mori cyclization with thionyl chloride led to the expected pyrrolo[1,2,3]thiadiazoles, again under aromatization, the low yields of the products obtained after tedious work-up were disappointing. Unfortunately, the yields fell even under 10% when the reaction was tried on a larger scale (> 1 g) (Scheme 22).

To prove our assumption, that the presence of the strongly basic amidrazone moiety could be the reason for these low yields, we used a *N*-methoxycarbonyl-protected pyrrolidinethione first in a model reaction. The sequence outlined in Scheme 23 led us to the parent system of pyrrolo[2,3-*d*][1,2,3]thiadiazole. It is noteworthy that the condensation with ethyl carbazate in this case was working perfectly also without any mercury salt.

Scheme 22



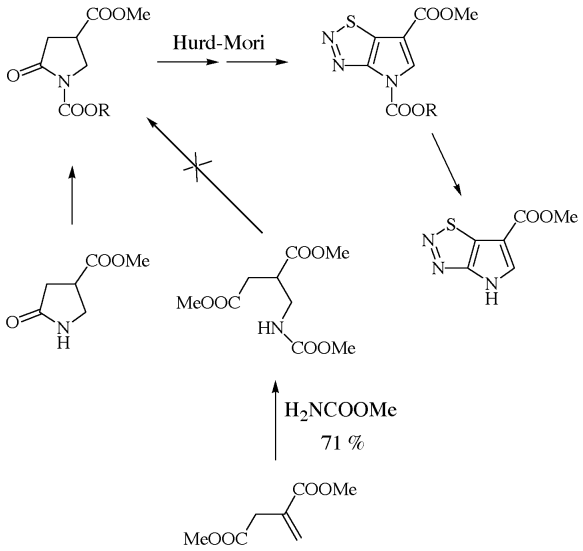
Scheme 23



The key-intermediate for the construction of our real target bearing the ester group was 5-oxo-pyrrolidine-1,3-dicarboxylate, not known from the literature. A direct pathway was envisioned firstly *via* base-catalyzed addition of methyl carbamate to dimethyl itaconate. Although the addition was working well, we failed later on in the cyclization step. As the unprotected lactam ester according to the literature was available simply by treatment of dimethyl itaconate with ammonia the desired compound should be available *via* subsequent acylation (Scheme 24). This cyclization was described by Wu *et al.* [16] in 1961 with a 50% yield, but unfortunately, we failed in all our attempts to reproduce this result, even when widely modifying the reaction parameters.

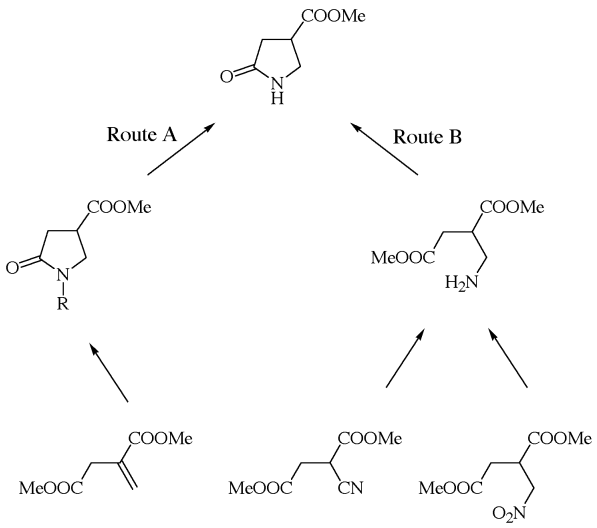
As other known synthetic pathways to access this product were enantioselective multistep syntheses using expensive reagents [17] we were interested in simple alternatives. Knowing that cyclization of dimethyl itaconate works excellent with primary amines, we were looking for suitable *N*-substituents easily removable after cyclization (Scheme 25, Route A). Another possi-

Scheme 24



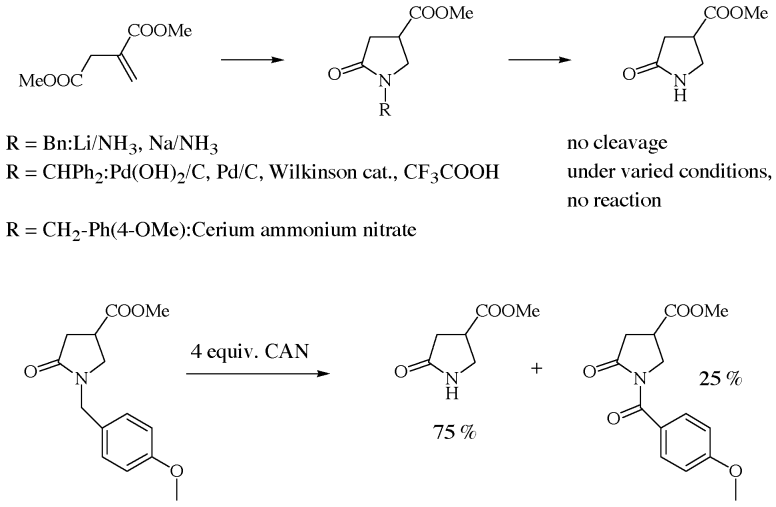
bility was considered in the cyclization of dimethyl 2-aminomethylsuccinate which should be available by hydrogenation of 2-nitromethylsuccinate or 2-cyanosuccinate (Scheme 25, Route B).

Scheme 25



Attempted cleavage of the benzyl group under modified Birch conditions, hydrogenolysis of the diphenylmethyl group with a variety of catalysts as well as its acid-catalyzed deprotection with trifluoroacetic acid were all unsuccessful (Scheme 26). Oxidative cleavage of the 4-methoxybenzyl group with cerium ammonium nitrate was working well and led to a mixture of benzaldehyde, the *N*-benzoyl compound and the desired deprotected product. Due to the high water solubility of the product, its separation from the large amount of existing inorganic material was tedious and not practically achievable, especially not when working on a larger scale.

Scheme 26

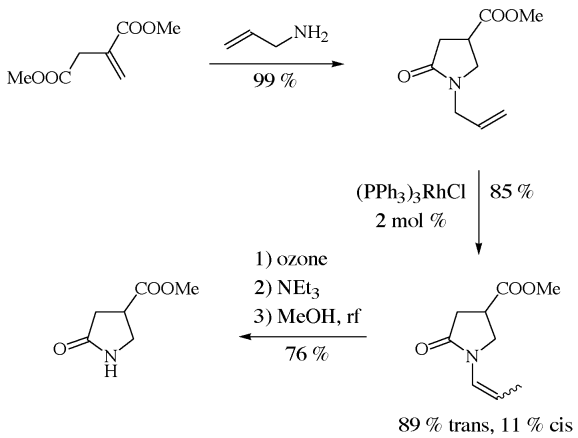


Changing the strategy, we tried to use an allyl group now for *N*-protection which after moving the double bond into *N*-conjugation under palladium-catalysis should be easily removable *via* ozonolysis of the enamide and spontaneous decarboxylation of the intermediate carbamic acid. The *N*-allyl-pyrrolidone was easily available and a series of optimization experiments led to the isolation of 85% of the rearranged product by using 2 mol % of Wilkinson catalyst giving better results then various palladium catalysts (Scheme 27). This was the first feasible approach for the preparation of gram quantities of the desired key-product. On the other hand, the catalyst is expensive and therefore we tried the already mentioned approaches of Route B next (Scheme 28).

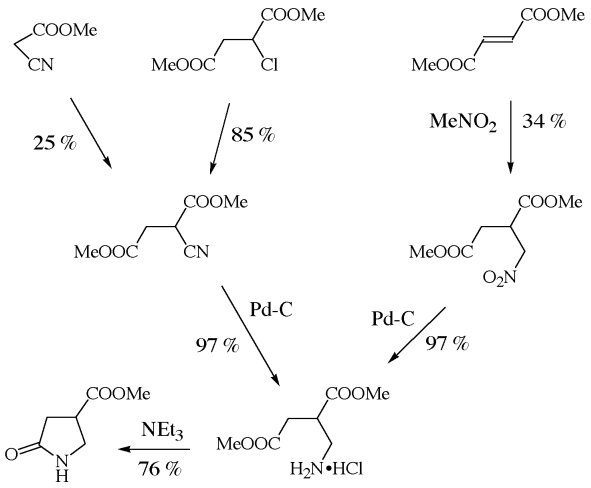
Alkylation of methyl cyanoacetate with methyl chloroacetate under phase-transfer conditions is known from the literature, but due to double alkylation the yield of the desired monoalkylation product is just 25% [18]. Dimethyl cyanosuccinate is also available starting from aspartic acid *via* reaction of 2-chlorosuccinate with sodium cyanide [19]. It can be hydrogenated quantitatively to the desired dimethyl 2-aminomethylsuccinate which can be stored as hydrochloride. An even shorter and very convenient approach was later found in the addition of nitromethane to dimethyl fumarate, again under phase-transfer conditions. This reaction up to now only led to 34% yield, but the starting products can easily be recycled thus attributing economic advantage to this method. The hydrogenation of the nitro group was achieved at 5 bar hydrogen pressure and the cyclization occured after addition of triethylamine under reflux conditions in methanol. Now we had a good method for the synthesis of this key intermediate and finally we could start with the construction of our pyrrolo[2,3-*d*]-[1,2,3]thiadiazole system *via* the Hurd-Mori reaction.

Thionation with Lawesson´s reagent led to the thiolactam in an excellent yield (Scheme 29). Introduction of the protecting group was accomplished with methyl chloroformate or di-*tert*-butylpyrrocarbonate, respectively.

Scheme 27

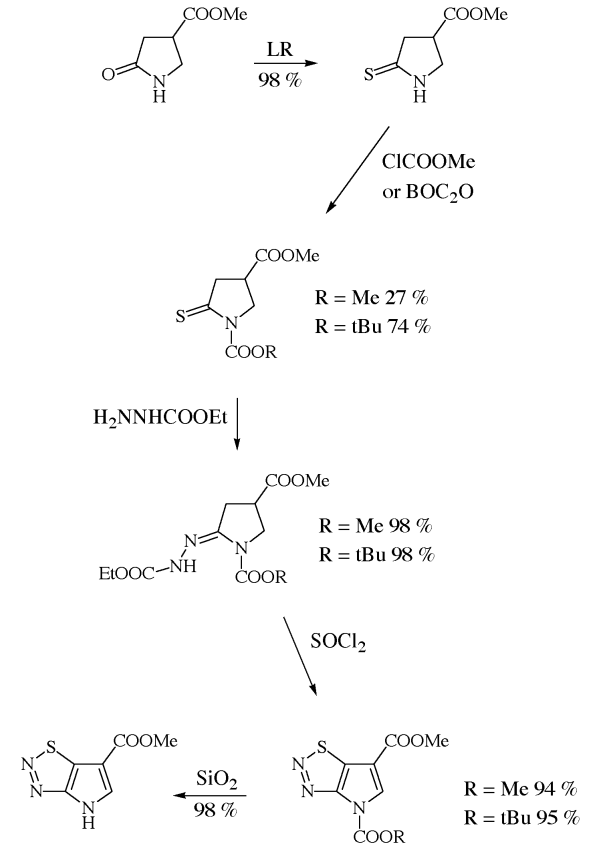


Scheme 28



Condensation with ethyl carbazate led to the amidrazone intermediates which were then cyclized with thionyl chloride without further purification of the intermediates. The result of the cyclization was again the expected, fully aromatized dimethyl pyrrolo[2,3-*d*][1,2,3]thiadiazole-4,6-dicarboxylate in excellent yields. Cleavage of the *N*-protecting group was accomplished simply by stirring the product with silica gel or with trifluoroacetic acid in methylene chloride, respectively. Comparing the yields of this sequence with those of our first efforts to synthesize the methyl or benzyl compounds, this result can be considered as the happy end of the story.

Scheme 29



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