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The Chemistry of Benzothiadiazole Plant Activators*

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Abstract: Systemic Acquired Resistance (SAR) is an inducible resistance mechanism in plants that, together with other defence mechanisms, provides broad-spectrum and long-lasting disease control. With novel screening techniques the benzo[1,2,3]thiadiazole-7-carboxylic acid derivatives have been identified as a new class of chemicals which stimulate the plant's own defence mechanisms. The synthesis and biological activities of various benzo[1,2,3]thiadiazoles and related structures are described. *S*-Methyl benzo[1,2,3]thiadiazole-7-carbothioate is the first synthetic chemical 'plant activator' that has been developed for this novel disease control concept.

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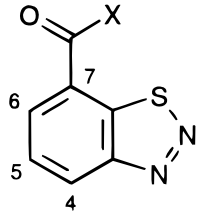
Key words: Systemic Acquired Resistance (SAR), plant activator, benzo[1,2,3] thiadiazole, plant protection, immunisation, defence mechanisms

1 INTRODUCTION

In modern pest management it has become ever more important to find new crop protection chemicals with novel modes of action.[1] Nearly all fungicides are based on a direct antibiotic principle. A new potential concept for chemically mediated disease control is based on compounds which activate the plant's own 'immune system'. The induction of disease resistance in plants is called 'systemic acquired resistance' (SAR). Plants, when locally infected with a necrotising pathogen or non-pathogen, often develop a long-lasting, broad-spectrum 'immunity' against subsequent infection.[2,3] Based on natural defence mechanisms of plants SAR is very interesting as an additional option for disease control. However, naturally induced SAR is not predictable in timing and level of expression and therefore has not been used in crop protection to date. Using special screening procedures, we were able to identify chemicals which activate the SAR response in plants. Chemicals which are considered 'plant activators' have no direct antimicrobial activity. They induce resistance to the same spectrum of pathogens as in the biological model and lead to expression of the same biochemical markers, such as the PR-proteins, in the plant. The discovery of 'plant activating' compounds such as 2,6-dichloro-isonicotinic acid (CGA 41396)[4–6] and benzo[1,2,3]thiadiazole-7-carboxylic acid derivatives has not only led to the first commercial 'plant activator' CGA 245704 (Fig. 1, **1**) but has also stimulated the study of the biochemical[7–10] and genetic[11–13] basis of plant



1 X = SCH_3 (CGA 245704)
2 X = OCH_3
3 X = OH

Fig. 1. The benzo[1,2,3]thiadiazole-7-carboxylic acid lead structure.

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immunity. This paper describes the synthesis and biological activity of benzo[1,2,3]thiadiazole-7-carboxylic acid derivatives and related compounds.

2 DISCOVERY AND SYNTHESIS OF BENZO[1,2,3]THIADIAZOLE-7-CARBOXYLIC ACID DERIVATIVES

In the course of a synthesis project directed towards sulfonylurea herbicides the reaction of 2-benzylthio-3-methoxycarbonylbenzenediazonium chloride with furan was attempted. However, instead of the desired 2-benzylthio-3-furanylbenzoic acid methyl ester, benzo[1,2,3]thiadiazole-7-carboxylic acid methyl ester (**2**) was isolated. This type of benzothiadiazole formation (see also Fig. 2) has already been reported in the literature[14] as well as the compound **2** itself.[15] In our screening, however, **2** was discovered to trigger SAR in plants.

Benzo[1,2,3]thiadiazole-7-carboxylic acid **3**, the key intermediate for the synthesis of various carboxylic acid derivatives, is best prepared by two known methodologies for the synthesis of thiadiazoles (Fig. 2):

(a) cyclisation of the diazonium salt of a 2-alkylthio-3-aminobenzoic acid derivative of the general formula **4**,[16] or

(b) cyclisation of a *N*-acyl- or *N*-tosylhydrazone **5** bearing an adjacent α-methylene group by treatment with thionyl chloride (Hurd Mori reaction),[17,18] followed by spontaneous aromatisation of the intermediate **6** with subsequent transformation to the carboxylic acid **3**.

The first synthesis of **3** (Fig. 3) started with the esterification of 2-chloro-3-nitrobenzoic acid **7** to the corresponding methyl ester **8**. Substitution of chlorine by benzylmercaptan gave the intermediate **9**, which on reduction in tetrahydrofuran led to methyl-3-amino-2-benzylthiobenzoate **10** which was cyclised by diazotisation to methyl benzo[1,2,3]thiadiazole-7-carboxylate **2**. Hydrolysis yielded the desired carboxylic acid **3**.

However, since the 1,2,3-trisubstituted benzoic acid system **7** was not accessible by selective mononitration, we developed a method[19] which led to methyl 2-benzylthio-3,5-diaminobenzoate **14** (Fig. 4) in a one-pot procedure, starting with 2-chloro-3,5-dinitrobenzoic acid **11**. Cyclisation and *in situ* reduction of the diazonium group in the 5-position (**15**) using phosphinic acid yielded the methyl ester **2** which was hydrolysed to the acid **3**. Various carboxylic acid derivatives **17** were prepared *via* the corresponding acid chloride **16**.

A third synthetic approach to the carboxylic acid **3** started with 1,2-dichloro-3-nitrobenzene **18** (Fig. 5). Substitution of chlorine in the 2-position by isopropyl mercaptan led to the intermediate **19**, which was reduced to 3-chloro-2-isopropylthioaniline **20**. Substitution of the second chlorine by a cyano group to yield the nitrile **21** was achieved in the presence of a nickel

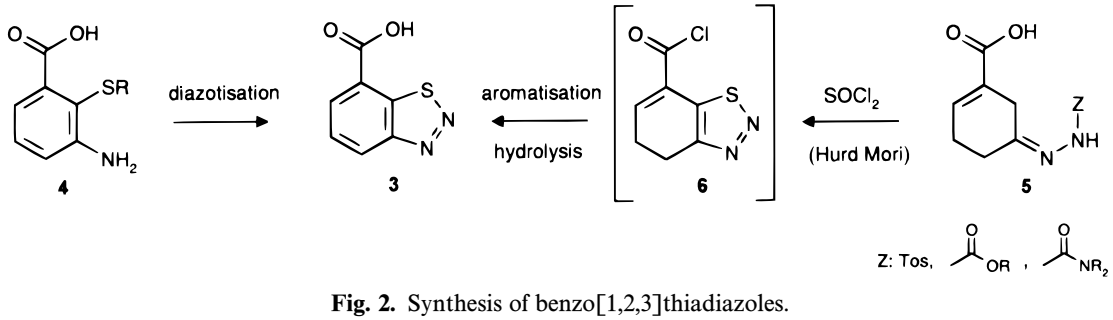

Fig. 2. Synthesis of benzo[1,2,3]thiadiazoles.

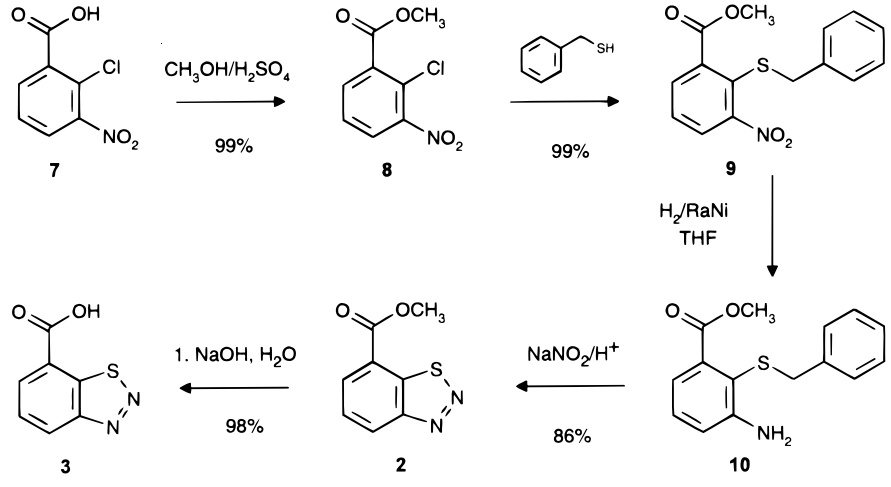

Fig. 3. Synthesis of benzo[1,2,3]thiadiazole-7-carboxylic acid **3**.

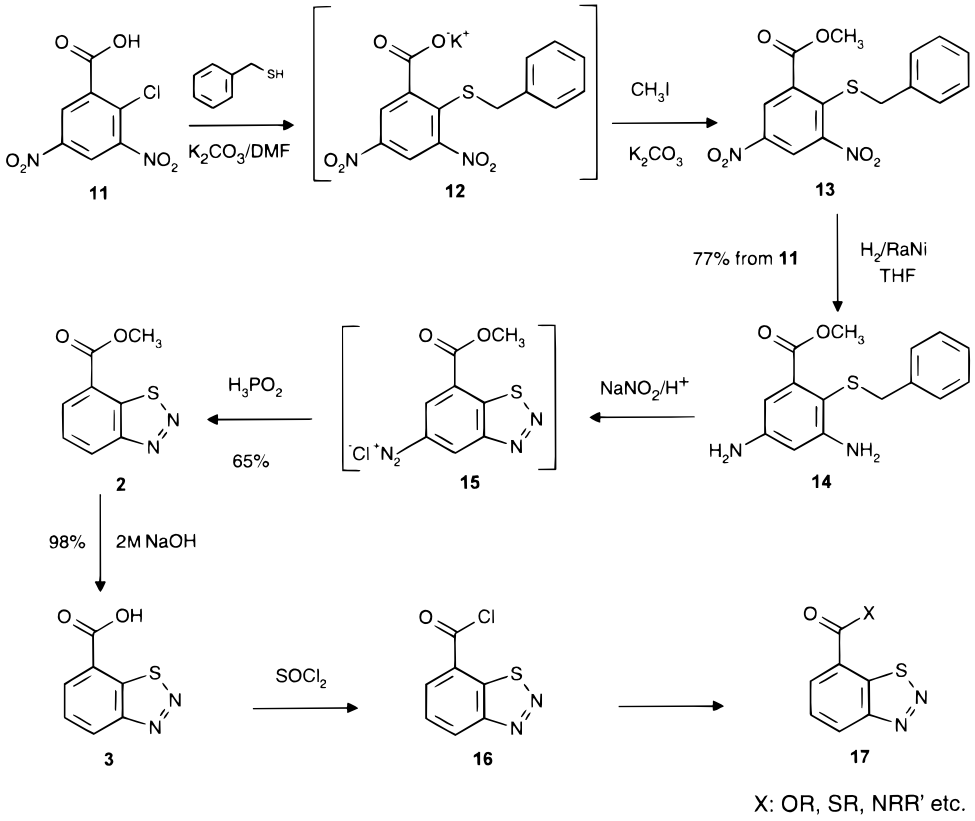

Fig. 4. Synthesis of benzo[1,2,3]thiadiazole-7-carboxylic acid derivatives starting from 2-chloro-3,5-dinitrobenzoic acid.

catalyst.[20] Subsequent cyclisation to benzo[1,2,3]-thiadiazole-7-nitrile **22** followed by hydrolysis yielded the corresponding carboxylic acid **3**.

A further strategy (see also Fig. 2) for the synthesis of benzo[1,2,3]thiadiazole-7-carboxylic acid derivatives uses the Hurd-Mori cyclisation methodology[17,18] *via* non-aromatic intermediates (Fig. 6). 3-Oxo-1-cyclohexene-1-carboxylic acid **24** was prepared[21] by Birch reduction of *m*-anisic acid **23** and transformed into the corresponding tosyl hydrazone **25**. Cyclisation with thionyl chloride led to the intermediate **26**, which under the reaction conditions underwent spontaneous aromatisation to the corresponding benzo[1,2,3]thiadiazole **16**. This intermediate was quenched with methylmercaptan to yield directly the carbothioic acid *S*-methyl ester **1**. During chromatography no significant amount of any other regioisomer of **1** was isolated.

3 BIOLOGICAL RESULTS AND STRUCTURE-ACTIVITY RELATIONSHIP

In our study of the structure–activity relationships of benzo[1,2,3]thiadiazoles and related molecules, we envisaged three structural elements of the benzothiadiazole nucleus **27** for chemical exploration, as exemplified by the representative structures shown in Fig. 7:

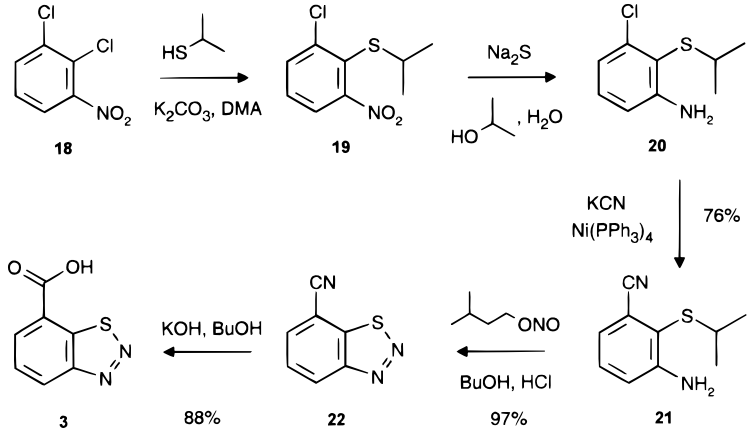

Fig. 5. Synthesis of benzo[1,2,3]thiadiazole-7-carboxylic acid starting with 2,3-dichloronitrobenzene.

(a) variation of the substituent at the 7-position of the benzothiadiazole nucleus **27** (**17a–e**, **28**, **32–41**),
(b) variation of the substitution pattern on the phenyl ring of the benzothiadiazole nucleus (**29–31**, **42—44**),
(c) variation of the heterocyclic five-membered ring system of the benzo[1,2,3]thiadiazole carboxylic acid **3** (**45–53**).

All compounds were tested *in vivo* for activation of resistance in cucumber plants against *Colletotrichum lagenarium* (Paserini) Ell. & Halst. Two-week-old cucumber plants were sprayed with a wettable powder formulation of the test compound at 200 mg AI kg^{-1}. After 72 h the plants were infected with a spore suspension ($1{\cdot}0 \times 10^5$ spores ml^{-1}) of *C. lagenarium* and incubated for 30 h at high humidity in the dark at a temperature of 23°C. Incubation was then continued at normal humidity in the greenhouse at 22° to 23°C. The infected leaf area was determined by visual assessment seven to eight days after inoculation. Other patho systems such as *Pseudomonas lachrymans* Carstner/cucumber, *Erysiphe graminis* DC/wheat and *Phytophthora infestans* (Mont) de Bary/tomato were also tested. However, in our experience, the cucumber system is representative of the general biological activity for these plant activators. Compounds which showed good biological activity in the greenhouse were then tested in field trials for protection of wheat against *E. graminis*, rice against *Pyricularia oryzae* Cav. and tobacco against *Peronospora tabacina* Adam.

Investigation of these structures highlighted the following key points:

1. The unsubstituted benzo[1,2,3]thiadiazole **27** as well as its 7-methyl derivative **28** were biologically inactive.
2. The position of the carboxylic acid function on the phenyl ring was critical for biological activity: In contrast to the lead structure **3**, compounds **29**, **30** and **31** and their carboxylic acid derivatives had no resistance-inducing activity.
3. Within the series of mono-substituted benzo[1,2,3]-thiadiazoles (**17a–e**, **28**, **32–41**), the 7-carboxylic acid derivatives **17a–e** displayed a high resistance-inducing activity whereby esters (**17a**), thiolesters (**17b**) and hydrazides (**17e**) were better than amides (**17d**) depending on the alkyl substituent R. In general, the higher the molecular weight of the carboxylic acid derivative, the lower the activity. Benzothiadiazoles with a sulfonic acid (**32**), sulfonamide (**33**) or phosphinic acid (**34**) functionality in the 7-position were inactive, as was the nitro compound **35**. The homologous carboxylic acid **36** was inactive, whereas the vinylogous derivative **37** had moderate activity.
4. The corresponding carboxaldehyde **38** and its acetals (**39**) as well as the corresponding carbinol **40** and its *O*-acyl or *O*-alkyl derivatives (**41**) were less active than the carboxylic acid **3** or the *S*-methyl ester **1**.
5. Additional substituents in position 4, 5 or 6 of the phenyl ring (**42–44**) generally decreased the activity. The resistance-inducing activity of benzo[1,2,3]-thiadiazole-7-carboxylic acid derivatives halogenated in position 4, 5 or 6 (**42**) was in the order F > Cl > Br. Fluorinated compounds were nearly as active as the non-substituted analogues, whereas brominated derivatives were inactive. Substituents such as hydroxy-, acyloxy- or methoxy- on the phenyl ring led to biologically inactive compounds. Molecules such as **43** or **44** and their carboxylic acid derivatives with a second annelated ring system in the 4, 5 position were inactive.
6. Replacement of the benzo[1,2,3]thiadiazole nucleus by other benzo-condensed heterocyclic five-membered ring systems generally led to inactive compounds (**45–53**). Even the corresponding benzo[2,1,3]thiadiazole-7-carboxylic acid derivatives (**45**) were biologically inactive, whereas the benziso-thiazole carboxylic acid derivatives (**46**) had moder-

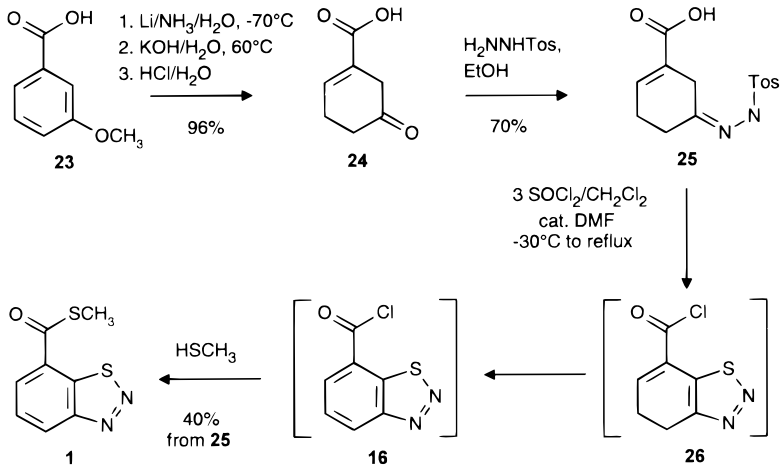

Fig. 6. Synthesis of **1** using the Hurd–Mori cyclisation methodology.

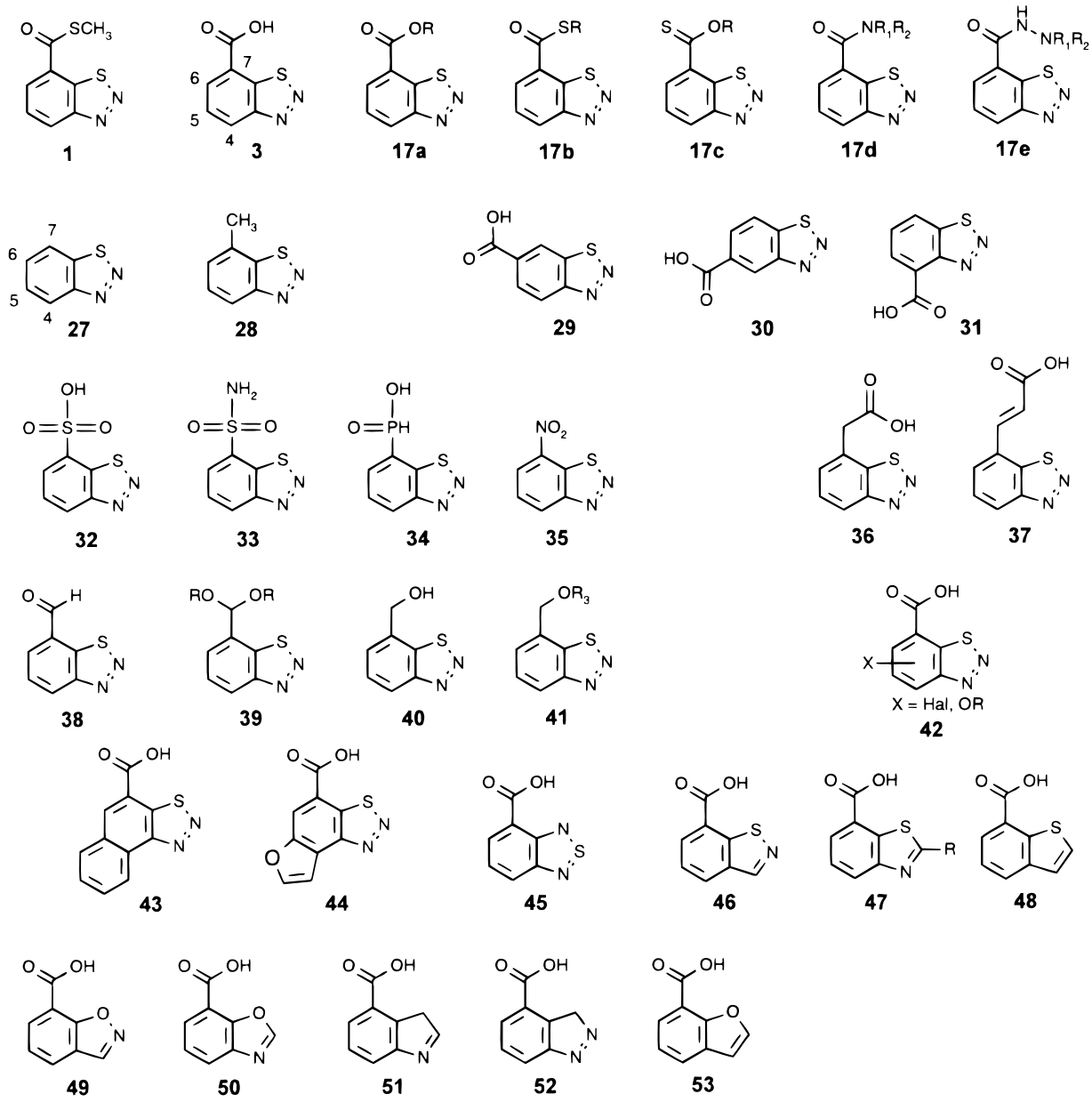

Fig. 7. Structural variations of the lead compound **3**. R, R_1, R_2 = alkyl; R_3 = alkyl, acyl.

ate activity. Benzo[1,2,3]oxadiazole is unstable except in the gaseous state, existing merely in the open zwitterionic form,[22] so synthesis of this system was not attempted.

4 SYNTHESIS OF [1,2,3]THIADIAZOLOPYRIDINE-7-CARBOXYLIC ACID DERIVATIVES

The variation of the phenyl moiety of the benzo[1,2,3] thiadiazolecarboxylic acid was an interesting challenge from a synthetic point of view. The synthesis of key pyridine intermediates with the appropriate substitution pattern for diazotisation and cyclisation to the corresponding 7-[1,2,3]thiadiazolopyridine-7-carboxylic acid derivatives was achieved by the directed metallation protocol, a powerful methodology for regioselective efficient functionalisation of aromatic[23] and heteroaromatic compounds.[24] In the synthesis of structures **62** and **77** we used a *O*-thiocarbamate as a versatile *ortho*-directing group which could be transformed later into the corresponding *S*-thiocarbamate by a Kwart–Newman rearrangement.[25] Moreover the *S*-thiocarbamoyl group served as a useful protecting and leaving group in the cyclisation step.[26]

Thus transformation of 3-hydroxypicolinic acid **54** to the methyl ester **55** (Fig. 8) followed by aminolysis with diethylamine led to the corresponding diethylamide **56** which was coupled with diethylthiocarbamoyl chloride[27] to give the intermediate **57**. *Ortho*-lithiation

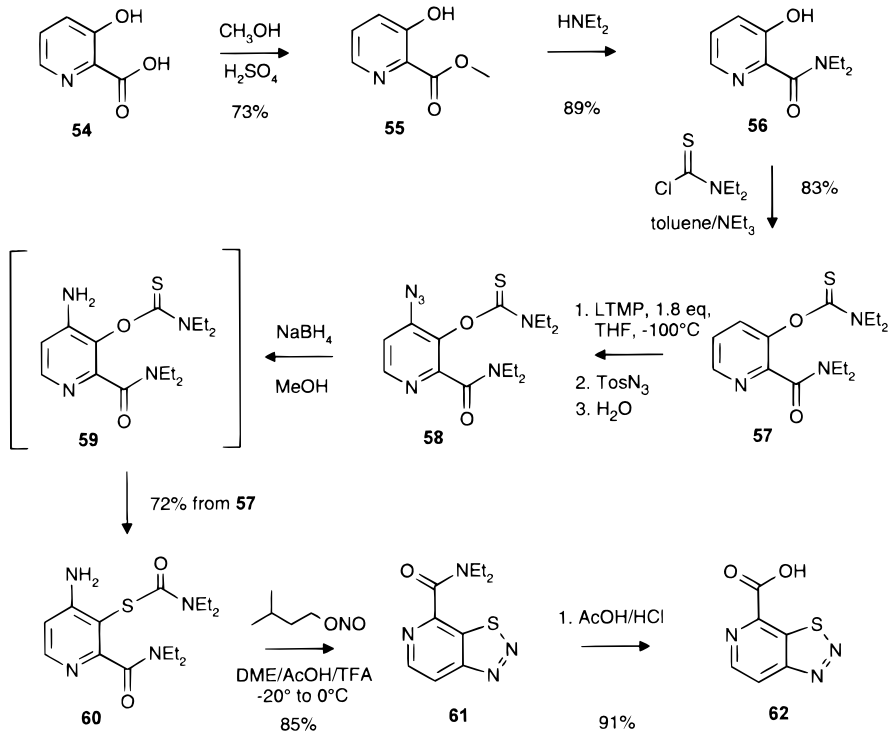

Fig. 8. Synthesis of [1,2,3]thiadiazolo[5,4-*c*]pyridine-7-carboxylic acid.

with lithium-2,2,6,6-tetramethylpiperidide (LTMP) at −100°C followed by reaction with tosylazide yielded crystalline azide **58**. The metallation step had to be carried out at −100°C because of the competitive anionic *ortho*-Fries rearrangement even at −78°C.[25] For complete lithiation, 1·8 equivalents of LTMP were necessary. The reduction step generated directly the rearranged product **60**. Cyclisation to pyridothiadiazole **61** was performed with isoamyl nitrite under anhydrous conditions in the presence of acetic acid serving to cleave the *S*-thiocarbamoyl group.[28] Hydrolysis of the diethylamine **61** furnished [1,2,3]thiadiazolo[5,4-*c*] pyridine-7-carboxylic acid **62**.

The synthesis of pyridothiadiazole **68** (Fig. 9) started with 5-bromonicotinic acid **63** which was converted to the corresponding diethylamine **64** and metallated with lithium diisopropylamide (LDA) in the presence of dibenzyl disulfide at −78°C to give the intermediate **65**. Transformation into the corresponding 5-amino-4-benzylthionicotin amide **66** followed by cyclisation with isoamyl nitrite under anhydrous conditions yielded the pyridothiadiazole **67**, which was hydrolysed to the corresponding [1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxylic acid **68**.

The synthesis of [1,2,3]thiadiazolo[4,5-*b*]pyridine-7-carboxylic acid **77** (Fig. 10) started with the lithiation of 2-fluoropyridine **69** and reaction with boronic acid trimethyl ester followed by aqueous work-up to give the boronic acid **70**. Oxidation yielded 2-fluoro-3-hydroxypyridine **71**, which was coupled with diethylthiocarbamoyl chloride to give the *O*-thiocarbamate **72**. A second metallation step and reac-

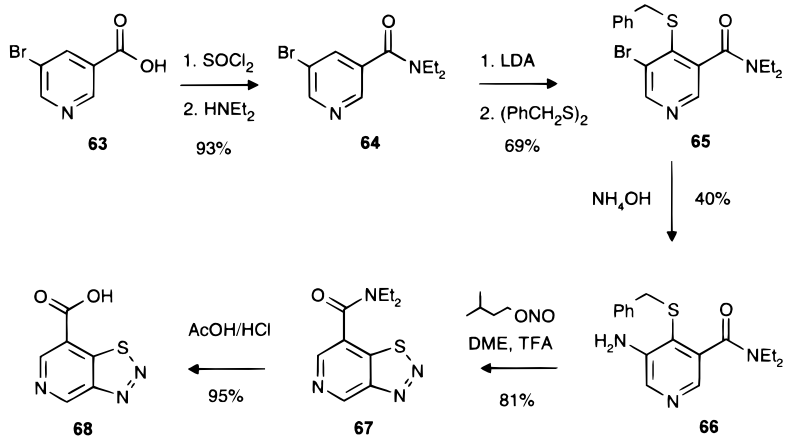

Fig. 9. Synthesis of [1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxylic acid.

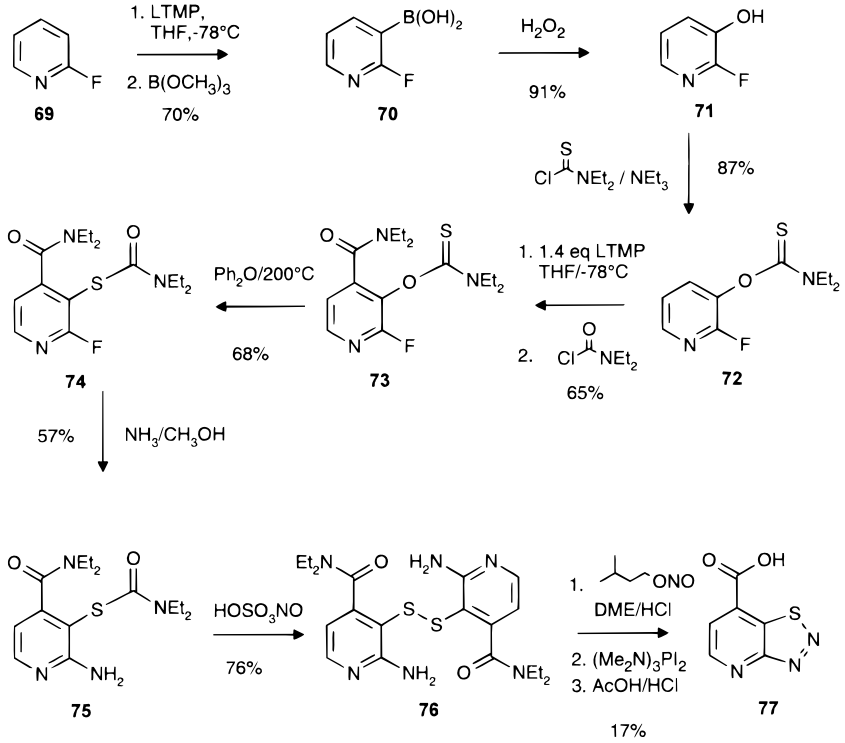

Fig. 10. Synthesis of [1,2,3]thiadiazolo[4,5-*b*]pyridine-7-carboxylic acid.

tion with diethylcarbamoyl chloride yielded the isonicotinic acid derivative **73**. Kwart–Newman rearrangement at 200°C to the *S*-thiocarbamate **74** followed by treatment with methanolic ammonia at 100°C in an autoclave yielded the appropriate starting material **75** for cyclisation. The diazotisation step failed with isoamyl nitrite in dimethoxyethane and acetic acid as a catalyst. Treatment with nitrosyl sulfuric acid in concentrated sulfuric acid generated the disulfide **76**. This intermediate now could be cyclised with isoamyl nitrite to a pyridothiadiazole-*N*-oxide which was reduced and hydrolysed to give finally the desired carboxylic acid **77**.

The biological activity of the [1,2,3]thiadiazolopyridine-7-carboxylic acid derivatives was dependent on the position of the nitrogen atom in the pyridine ring. The [1,2,3]thiadiazolo[5,4-*c*]pyridine-7-carboxylic acid **62**, [1,2,3]thiadiazolo[4,5-*b*]pyridine-7-carboxylic acid **77** and derivatives thereof are plant activators whereas the [1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxylic acid **68** and its derivatives were biologically inactive in our tests.

5 CONCLUSIONS

We have demonstrated that induction of SAR in plants by chemicals is a new and interesting option for disease control. As a result of novel approaches in random screening the benzo[1,2,3]thiadiazole-7-carboxylic acid derivatives were discovered as a new class of compounds which activate the SAR response in plants. The synthesis and testing of a large number of chemically modified compounds has led to a structure-activity profile of benzo[1,2,3]thiadiazoles and related structures as 'plant activators'. Based on the biological properties and the best overall field performance, *S*-methyl benzo[1,2,3]thiadiazole-7-carbothioate, **1** (CGA 245704) has been selected as the preferred disease control compound. It has been developed with the trade name 'Bion'® for agricultural practice. Ciba's 'plant activator' not only represents new chemistry in the agrochemical market, but even more a totally new technology and category of plant-protection agent.

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