An Improved Synthetic Approach to Thieno[2,3-*d*]-1,2,3-thiadiazole-carboxylates *via* Diazotization of Aminothiophene Derivatives

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The common synthetic method for the synthesis of fused 1,2,3-thiadiazoles *via* diazotization is not generally applicable to aminothiophenes. A substantially improved experimental protocol for the preparation of the title compounds as a potential inducer of systemic acquired resistance in plants is reported based on a novel cyclization mechanism *via* a Huisgen-White type rearrangement.

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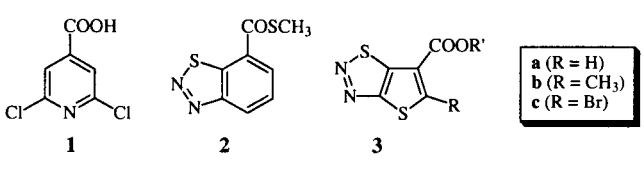
Introduction.

The concept of systemic acquired resistance represents a new approach in plant protection chemistry taking advantage of the plant's own defense mechanisms. A local infection of a plant can lead to the development of a certain resistance to subsequent challenges by a variety of pathogens. This immunization reaction is a systemic effect throughout the whole organism and can be triggered in two ways: Infection of a plant stimulates the development of natural defense mechanisms in a way not yet completely understood. The same effects within the organism can be induced by treatment of the plant with synthetic signal compounds. Both approaches lead to the same biochemical reactions in the plant strongly correlating with the expressions of PR-proteins [1]. Compounds like 2,6-dichloroisonicotinic acid **1**, various 1,2,3-benzothiadiazole-7-carboxylic acid derivatives such as **2** [2], or thiophene based thiadiazole systems of type **3** [3] (Scheme 1) are able to act as inducers of the systemic acquired resistance effect. The strategy of using these "plant activators" as systemic bioactive agents for the stimulation of the plant's inherent defense arsenal was successfully introduced as a new concept in plant protection chemistry by Novartis establishing acibenzolar-*S*-methyl (Bion®) (**2**) as the first commercial product.

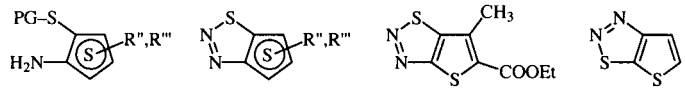
Scheme 1



1 **2** **3**

Recently we developed independent synthetic routes towards thieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylic acid derivatives **3** (R' = OH and OMe) [3]. Studying the synthetic method towards the thienothiadiazole system **B** *via* diazotization techniques of corresponding aminothiophene precursors **A** we faced some serious problems in the cyclization step (Scheme 2) [4]. Our conclusion that the intramolecular reaction of a sulfur functionality with an adjacent diazonium ion is highly dependent on the substitution of the thiophene core is in good agreement with the literature. While Gewald *et al.* reported good yields for the synthesis of the fully substituted system **4** [5], yields for the conversion of an amino precursor to unsubstituted **5** were only fair as stated by Paulmier [6]. A similar trend was observed by us for the cyclization towards heterocycles **3a** (R = H, 16% yield) and **3b** (R = Me, 55% yield), respectively [4].

Scheme 2



A **B** **4** **5**

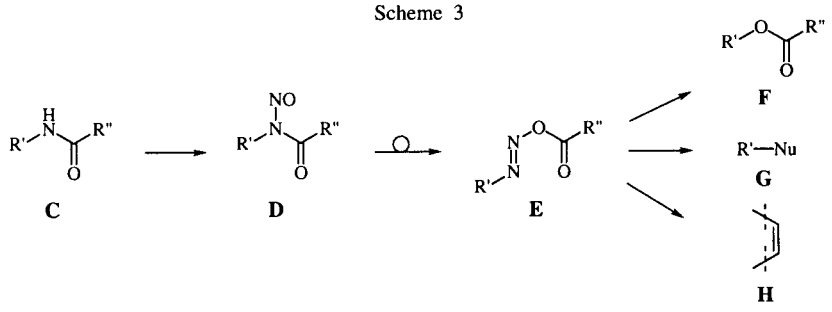
In an effort to improve the cyclization protocol on a general basis we tried to take advantage of the Huisgen-White rearrangement of acyl *N*-nitroso compounds **D** (Scheme 3). Formation of products **E** starting from amides or carbamates **C** proceeds under diazotization conditions placing a potential leaving group at the terminal nitrogen capable of further transformations. As a subsequent reaction evolution of nitrogen is possible to form an ester **F**. Both attack by a nucleophile to form compounds of type **G** as well as elimination towards an alkene **H** are accompanied by evolution of nitrogen and formation of the corresponding acid [7].

As an extension of this methodology we started to investigate the possibility of a nucleophilic attack at the terminal nitrogen avoiding the evolution of nitrogen gas. As a consequence the leaving group capability of the former *N*-protecting group could be used for the synthesis of the fused thiadiazole ring system **3** in an intramolecular cyclization reaction.

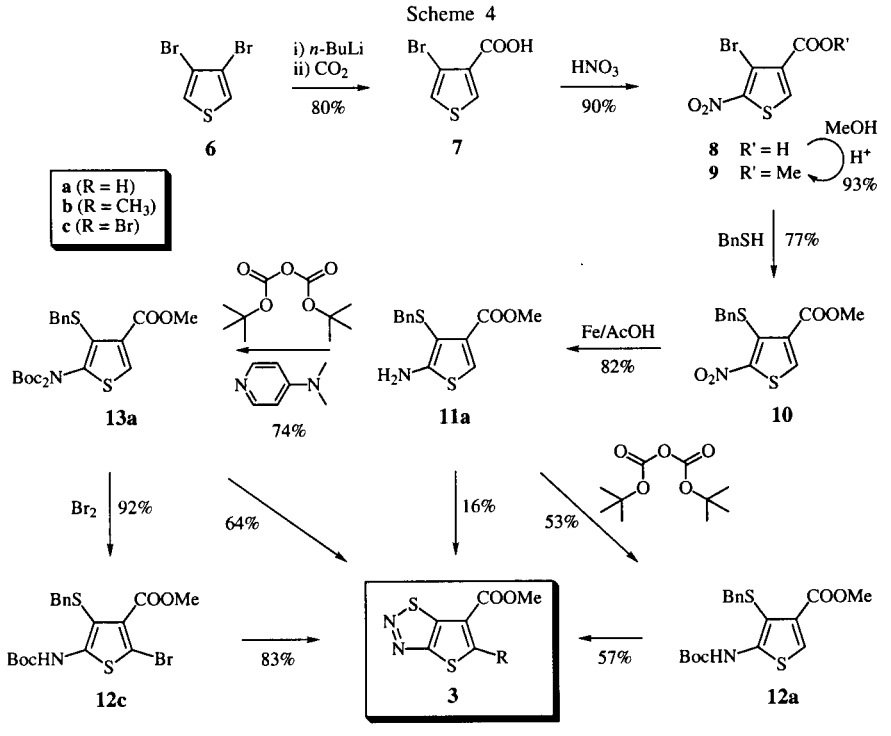
Results and Discussion.

The synthesis of the protected amino species **11** was accomplished using a straight forward strategy (Scheme 4). We started the sequence by metal-halogen exchange of commercially available 3,4-dibromothiophene **6** and quenching the mono-lithio compound with

Scheme 3



Scheme 4



carbon dioxide gas to give the acid **7** [8]. Introduction of the nitrogen functionality was performed by subsequent nitration with nitric acid/sulfuric acid to give compound **8** as a single isomer [8]. Protocols for both reactions were improved increasing the yields significantly compared to earlier reports in the literature. Esterification under acidic conditions gave product **9** [9] almost quantitatively representing a highly activated substrate for nucleophilic introduction of a protected sulfur functionality. Hence, treatment of **9** with benzylthiol in the presence of a base led to compound **10** which was converted to the amine **11a** (R = H) by reduction with iron [4].

Protection of the nitrogen with di-*tert*-butyl pyrocarbonate gave a mixture of **12a** (R = H) as major product accompanied by small amounts of the *bis*-protected product **13a**. Cyclization precursor **13a** was synthesized in good yield by treatment of **11a** with di-*tert*-butyl pyrocarbonate in the presence of 4-dimethylaminopyridine as catalyst [10].

In order to be able to compare the effect of the protective group on the cyclization reaction for both cases with or without a substituent in the 5-position of the resulting thienothiadiazole **3** we introduced an additional group into compound **13a**. Addition of bromine followed by mono-deprotection in a one-pot reaction gave precursor **12c** (R = Br) from **13a** in excellent yield.

The results of the cyclization of substrates **11**, **12**, and **13** *via* a Huisgen-White type rearrangement mechanism are summarized in the following table together with data from earlier reactions using classic diazotization techniques. In the case of the target molecule without substitution at the 5-position both butoxycarbonyl- (**12a**) and *bis*-butoxycarbonyl-protected (**13a**) precursor (entries 3 and 4) gave a 3.5-4 fold increase in yield compared to the amino precursor **11a** (entry 1). In the case of **13a** cyclization is initiated by beforehand mono-deprotection under the acidic conditions employed.

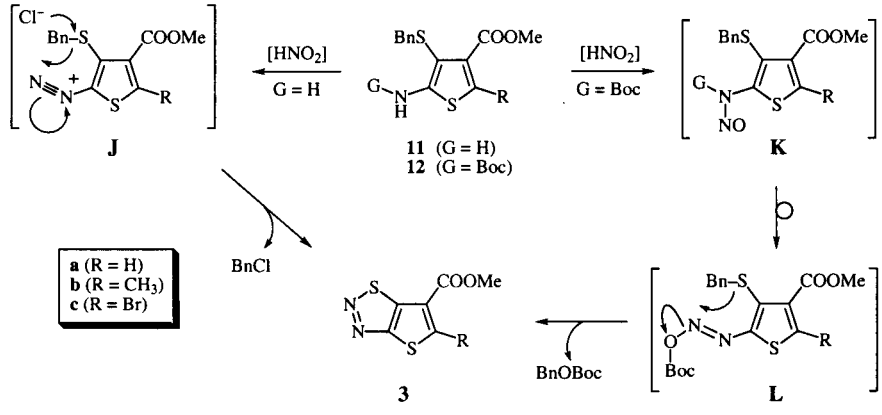
Table

Cyclization towards Thieno[2,3-*d*]-1,2,3-thiadiazoles **3**

entry	precursor	R	G	product	yield [%]
1	**11a**	H	H	**3a**	16 [4]
2	**11b**	Me	H	**3b**	55 [4]
3	**12a**	H	*tert*-butoxycarbonyl	**3a**	57
4	**13a**	H	*tert*-butoxycarbonyl	**3a**	64
5	**12c**	Br	*tert*-butoxycarbonyl	**3c**	83

Results obtained with fully substituted precursors indicate that potential side reactions can be minimized utilizing the Huisgen-White type method hence improving the yield of the fully substituted compound **3c** (entry 5) compared to the synthesis of **3b** (entry 2) under classical diazotization conditions.

Scheme 5



The improvements can be rationalized by comparing the intermediates of the cyclization for both the Huisgen-White type reaction and the diazotization: In the latter case a highly polarized cationic species **J** is formed representing a hard center and hence causing severe problems when the 2-position is not blocked (Scheme 5). This moiety is susceptible to a variety of side reactions as indicated in the literature in similar reactions at the electron rich thiophene core [11]. In contrast, the nitrogen carrying a leaving group in species **L** formed by rearrangement from **K** represents a soft center. Intramolecular attack of the adjacent sulfur proceeds more easily allowing less side reactions. The benzyl cation split-off is subsequently trapped by chloride in the diazotization sequence or by the leaving carbonate in the Huisgen-White type reaction.

EXPERIMENTAL

General.

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Dry methylene chloride was prepared by distillation from phosphorus pentoxide, dry tetrahydrofuran and diethyl ether by distillation from sodium/benzophenone, and dry methanol by distillation from magnesium. Commercially available dry dimethylformamide was treated with molecular sieves (4Å). *n*-Butyllithium was obtained from Aldrich as a 2.5*M* solution in hexane. Flash column chromatography was performed on silica gel 60 from E. Merck (40-63 μm, 9385) and tlc on Merck precoated silica gel plates (5554). In some cases the silica gel used was treated with a 10% solution of triethylamine in methylene chloride and dried *in vacuo* (triethylamine treated silica gel). Melting points were determined using a Kofler micro hot stage apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory, University of Vienna. The nmr spectra were recorded on a Bruker AC 200 (200MHz) spectrometer; chemical shifts are reported in ppm using tetramethylsilane as internal standard.

4-Bromo-3-thiophenecarboxylic Acid (**7**).

3,4-Dibromothiophene (50.00 g, 206.7 mmoles) was dissolved in dry diethyl ether (375 ml) with nitrogen and cooled to -85°. *n*-Butyllithium (1 equivalent) was added under mechanical stirring maintaining the temperature below -75 ±5° and the solution was stirred for 20 minutes. After the reaction mixture had been cooled to -120 ±5° dry carbon dioxide gas was passed through the solution keeping the temperature below -70°. When the exothermic reaction ceased (approximately 10 minutes) the mixture became heterogeneous and was slowly warmed to room temperature maintaining a small flow of carbon dioxide gas. After hydrolysis with ice/water the mixture was extracted once with diethyl ether. Acidification of the aqueous layer with concentrated hydrochloric acid gave a colorless precipitate that was collected by filtration and dried followed by recrystallization from ethanol/water to give 34.00 g (80%) of **7** [8] as colorless crystals, mp 158-160°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.50 (d, J = 4Hz, 1H), 8.19 (d, J = 4Hz, 1H), 12.8 (bs, 1H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 109.6 (s), 126.2 (d), 131.3 (s), 135.1 (d), 162.2 (s).

4-Bromo-5-nitro-3-thiophenecarboxylic Acid (**8**).

4-Bromo-3-thiophenecarboxylic acid **7** (16.50 g, 79.69 mmoles) was slowly dissolved in 125 ml of concentrated sulfuric acid cooled to -20°. A solution of fuming nitric acid (1.1 equivalents) in 25 ml of concentrated sulfuric acid was added maintaining the temperature below -10° and stirring continued until tlc indicated complete conversion (approximately 3 hours). Hydrolysis with

ice/water gave an orange precipitate that was filtered and washed thoroughly with water. Recrystallization from ethanol/water yielded 17.98 g (90%) of **8** [8] as yellow crystals, mp 246-248°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.67 (s, 1H), ~15 (bs, 1H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 113.2 (s), 132.9 (s), 139.0 (d), 147.5 (s), 161.3 (s).

4-Bromo-5-nitro-3-thiophenecarboxylic Acid Methyl Ester (**9**).

4-Bromo-5-nitro-3-thiophenecarboxylic acid **8** (5.00 g, 19.84 mmoles) and concentrated sulfuric acid (1.1 equivalents) were dissolved in 50 ml of dry methanol and refluxed overnight. Hydrolysis with ice/water was followed by extraction with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Recrystallization of the crude product with diisopropyl ether gave 4.90 g (93%) of **9** [9] as colorless crystals, mp 124-125°; ^{1}H nmr (deuteriochloroform): δ 3.93 (s, 3H), 8.30 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 52.5 (q), 130.0 (s), 132.6 (s), 136.4 (d), 148.0 (s), 160.3 (s).

5-Nitro-4-(phenylmethyl)thio-3-thiophenecarboxylic Acid Methyl Ester (**10**).

A 10% solution of benzylthiol (1 equivalent) in dry dimethylformamide was treated with potassium carbonate (1 equivalent) at 0°. To this mixture a 10% solution of the precursor **9** (4.50 g, 16.91 mmoles) in dry dimethylformamide was added maintaining the temperature below 0°. After hydrolysis with ice/water upon complete conversion indicated by tlc the mixture was extracted with diethyl ether, the combined organic layers were washed with 2 *N* hydrochloric acid, saturated sodium bicarbonate-solution, and water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Recrystallization from diisopropyl ether gave 4.05 g (77%) of **10** [4] as yellow crystals, mp 75-77°.

5-(1,1-Dimethylethoxycarbonyl)amino-4-(phenylmethyl)thio-3-thiophenecarboxylic Acid Methyl Ester (**12a**).

A solution of **11a** (0.39 g, 1.40 mmoles) in 5 ml of dry tetrahydrofuran was added to a mixture of sodium hydride (1.2 equivalents) in 2 ml of dry tetrahydrofuran and stirred at room temperature for 30 minutes. Di-*tert*-butyl pyrocarbonate (1.1 equivalents) in 5 ml of dry methylene chloride was added and stirring was continued. Hydrolysis with water after complete conversion according to tlc was followed by extraction with diethyl ether. The combined organic layers were washed with saturated sodium bicarbonate solution and water, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography (triethylamine treated silica gel 20:1, petroleum ether:diethyl ether = 6:1) to give 0.30 g (53%) of **12a** as faint yellow crystals and 0.10 g (14%) of **13a** as a by-product, mp 92-95°; ^{1}H nmr (deuteriochloroform): δ 1.47 (s, 9H), 3.89 (s, 3H), 3.91 (s, 2H), 7.05 (m, 2H), 7.17 (m, 3H), 7.37 (bs, 1H), 7.63 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 28.0 (q), 40.8 (t), 51.6 (q), 81.6 (s), 107.9 (s), 123.9 (d), 127.0 (d), 128.2 (s), 128.6 (s), 131.3 (s), 138.2 (s), 146.5 (s), 151.5 (s), 162.7 (s).

Anal. Calcd. for $C_{18}H_{21}NO_4S_2$: C, 56.97; H, 5.58; N, 3.69. Found: C, 57.15; H, 5.44; N, 3.59.

5-[Bis(1,1-dimethylethoxycarbonyl)]amino-4-(phenylmethyl)-thio-3-thiophenecarboxylic Acid Methyl Ester (**13a**).

A solution of di-*tert*-butyl pyrocarbonate (2 eq) in 60 ml of dry methylene chloride was added to a mixture of **11a** (5.66 g, 20.26 mmoles), dry triethylamine (2 eq), and 4-dimethylaminopyridine (0.2 eq) in 100 ml of dry methylene chloride and refluxed until tlc indicated complete conversion. After the reaction mixture was cooled to room temperature hydrolysis with ice/water was followed by extraction with diethyl ether. The combined organic layers were washed with 2 *N* hydrochloric acid and water, dried over sodium sulfate, filtered, and evaporated. The crude oil was purified by flash column chromatography (triethylamine treated silica gel 30:1, petroleum ether : ethyl acetate = 15:1) to give 6.87 g (74%) of **13a** as yellow crystals, mp 80-83°; ^{1}H nmr (deuteriochloroform): δ 1.45 (s, 18H), 3.89 (s, 3H), 4.08 (s, 2H), 7.27 (m, 5H), 8.10 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 27.7 (q), 39.9 (t), 51.7 (q), 83.6 (s), 127.1 (d), 128.3 (d), 129.1 (d), 129.6 (d), 131.8 (d), 132.1 (s), 136.9 (s), 143.7 (s), 150.3 (s), 162.0 (s).

Anal. Calcd. for $C_{23}H_{29}NO_6S_2$: C, 57.60; H, 6.09; N, 2.92. Found: C, 57.82; H, 6.19; N, 3.19.

2-Bromo-5-(1,1-dimethylethoxycarbonyl)amino-4-(phenylmethyl)thio-3-thiophenecarboxylic Acid Methyl Ester (**12c**).

A solution of **13a** (2.40 g, 5.00 mmoles) in 25 ml of dry methylene chloride was added to bromine (1 equivalent) dissolved in 25 ml of dry methylene chloride at -40° and stirred for 45 minutes. The mixture was hydrolyzed with water and extracted with diethyl ether. The combined organic layers were washed with saturated sodium bicarbonate-solution and water, dried over sodium sulfate, filtered, and concentrated. The crude compound was purified by flash column chromatography (triethylamine treated silica gel 30:1, petroleum ether:ethyl acetate = 9:1) to give 2.12 g (92%) of **12c** as yellow crystals, mp 66-68°; ^{1}H nmr (deuteriochloroform): 1.41 (s, 9H), 3.85 (s, 2H), 3.90 (s, 3H), 6.92-7.25 (m, 5H); ^{13}C nmr (deuteriochloroform): 28.0 (q), 41.2 (t), 52.1 (q), 82.2 (s), 112.0 (s), 127.3 (d), 128.5 (d), 128.7 (d), 138.2 (s), 146.8 (s), 151.6 (s), 163.4 (s).

Anal. Calcd. for $C_{18}H_{20}BrNO_4S_2$: C, 47.16; H, 4.40; N, 3.06. Found: C, 47.10; H, 4.16; N, 2.86.

Cyclization to **3**. General Procedure.

An approximately 3% solution of the precursor **11, 12,** or **13** (1 equivalent) in a 1:1 mixture of acetic acid and concentrated hydrochloric acid was cooled below 10° and slowly treated with an approximately 10% solution of sodium nitrite (1.1 equivalents) in water. The progress of the reaction was monitored by tlc. After hydrolysis with ice/water the mixture was extracted with methylene chloride. The combined organic layers were washed with saturated sodium bicarbonate-solution and water, decolorized with charcoal, dried over sodium sulfate, filtered, and evaporated *in vacuo*.

Thieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylic Acid Methyl Ester (**3a**).

The *tert*-butoxycarbonyl protected precursor **12a** (200 mg, 0.53 mmole) gave 60mg (57%) of **3a** [4] after flash column chromatography (silica gel 30:1, petroleum ether : ethyl acetate = 5:1) according to the above general protocol.

The bis-*tert*-butoxycarbonyl compound **13a** (200 mg, 0.42 mmoles) was converted to 54 mg (64%) of **3a** [4] after chromatographic purification, mp 140-142°.

5-Bromothieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylic Acid Methyl Ester (**3c**).

Precursor **12c** (3.22 g, 7.02 mmoles) gave 1.63 g (83%) of **3c** as colorless crystals after chromatographic purification (silica gel

30:1, petroleum ether : methylene chloride = 7:3) according to the general cyclization procedure, mp 156-159°; ^{1}H nmr (deuteriochloroform): δ 4.00 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 52.9 (q), 121.0 (s), 131.2 (s), 145.6 (s), 158.8 (s), 160.3 (s).

Anal. Calcd. for $C_6H_3BrN_2O_2S_2$: C, 25.82; H, 1.08; N, 10.04. Found: C, 26.07; H, 1.21; N, 10.13.

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