Modifying the 5-Position of Thieno[2,3-*d*][1,2,3]thiadiazole-6-carboxylate Derivatives

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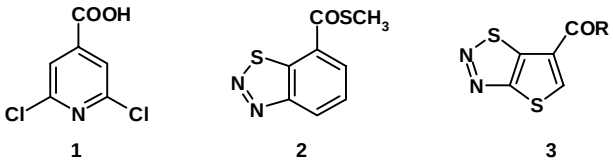
Abstract. Thieno[2,3-*d*][1,2,3]thiadiazole-6-carboxylates **3** belong to a new group of plant protecting agents as highly potent inducers of systemic acquired resistance (SAR). In order to obtain an enhanced basis set for structure activity relationship studies several modifications of the heteroaromatic core were performed by introduction of various substituents. One approach utilizing metallation techniques led to several 5-substituted derivatives **4a**–**h** of the title compound. Using the chloro-compound **5** obtained *via* this route the ability to undergo nucleophilic substitution reactions was investigated, representing a complementary strategy towards derivatives **6a**–**c**.

The phenomenon of "systemic acquired resistance" (SAR) can be triggered off in two ways: Local infection of a plant stimulates the development of natural defence mechanisms resulting in an immune reaction towards a variety of pathogens [1]. Essentially the same biochemical reactions within the organism can be induced by treatment of the plant with heterocyclic 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). The strategy of using these "plant activators" as systemic bioactive agents to stimulate the plant's inherent defence arsenal was successfully introduced as a new concept in plant protection chemistry by Novartis establishing Bion® (**2**) as the first commercial product [2].



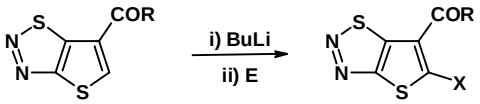
1 **2** **3**

Scheme 1

Recently, we developed two independent synthetic routes towards thieno[2,3-*d*][1,2,3]thiadiazole-6-carboxylates **3** (R = OH and OCH_3) *via* Hurd–Mori methodology [3] and diazotation techniques [4], respectively. Elaborating modifications of the hence easily accessible lead structure we were interested in introducing various substituents with different electronic and stereochemical properties into the 5-position of the heterocyclic system.

Results and Discussion

Out of the variety of general approaches to introduce functional groups into an aromatic core *ortho* lithiation represents a most versatile methodology [5]. Based on preliminary results from previous work [3] we started to study the metallation of both the free acid **3a** and the sterically hindered *tert*-butyl amide **3b** (Scheme 2). Compound **3b** was prepared in a straight forward way from the acid **3a** *via* the acid chloride and treatment with *tert*-butyl amine in expectedly high yields.



3 **a** (R=OH)
b (R=NH*tert*-Bu)

4a-h

entry	SM	E	procedure	product	R	X	yield (%)
1	**3a**	Cl_3CCCl_3	A	**4a**	OH	Cl	99
2	**3a**	I_2	A	**4b**	OH	I	60
3	**3a**	CH_3SSCH_3	A	**4c**	OH	SCH_3	74
4	**3a**	CH_3I	A/C	**4d**	OMe	CH_3	20
5	**3a**	DMF	A/C	**4e**	OMe	CHO	30
6	**3b**	DMF	B	**4f**	NH*tert*-Bu	CHO	50
7	**3a**	CO_2	A/C	**4g**	OMe	COOMe	41
8	**3b**	CO_2	B	**4h**	NH*tert*-Bu	COOH	66

Scheme 2

Best results for the metallation of the acid **3a** (R = OH) were obtained using LDA (general procedure A) whereas the amide **3b** (R = NH*tert*-Bu) was usually lithiated with *n*-BuLi (general procedure B) without decomposition of the base sensitive thiadiazole moiety [6]. A variety of electrophiles was successfully applied introducing both substituents with +I or +M-effects (Scheme 2, entries 1–4) and groups with –I/–M properties (Scheme 2, entries 5–8) into the 5-position. Due to the high polarity of products obtained from carboxylic acid **3a** isolation of some compounds caused problems (Scheme 2, entries 4, 5, 7). As a consequence the crude material was converted directly to the corresponding methyl ester (general procedure C). However, the overall yield *via* this two step procedure was usually lower than the conversion of the amide **3b** (Scheme 2, entries 6 and 8).

In a second approach the chlorocompound **5** [3] obtained by esterification *via* the DCC method was used as substrate

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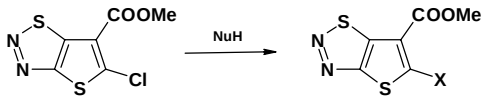

5 6a-d

entry	NuH	product	X	yield (%)
1	$PhCH_2SH$	**6a**	SCH_2Ph	80
2	pyrrolidine	**6b**		87
3	morpholine	**6c**		75
4	MeOH (+Na)	**6d**	OCH_3	0

Scheme 3

to investigate nucleophilic substitution at the heteroaromatic core (Scheme 3). Although the thiophene moiety represents an electron rich heterocycle the ester substituent together with the highly electron poor thiadiazole system enable attack at the 5-position. Both sulfur (Scheme 3, entry 1) and nitrogen substituents (Scheme 3, entries 2 and 3) were introduced with good to excellent yields, the latter being only somewhat tediously accessible *via* lithiation chemistry directly [7]. In contrast, conversion with oxygen nucleophiles (Scheme 3, entry 4) were unsatisfactory giving an unidentified variety of reaction products.

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Experimental

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Dry CH_2Cl_2 was prepared by distillation from P_2O_5, dry MeOH by distillation from Mg, and dry THF by distillation from sodium/benzophenone. Commercially available dry DMF was treated with molecular sieves (4 Å). *n*-Butyllithium was obtained from Aldrich as 2.5M solution in hexane. TLC was performed on Merck precoated silica gel plates (5554) and flash column chromatography on silica gel 60 from E. Merck (40–63 μm, 9385). Melting points were determined using a Reichert micro hot stage apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, University of Vienna. The NMR spectra were recorded on a Bruker AC 200 (200 MHz) spectrometer; chemical shifts are reported in ppm using Me_4Si as internal standard.

Lithiation of Carboxylic Acid 3a with LDA and Introduction of Electrophiles (General Procedure A)

A 10%(w/v) solution of dry diisoproylamine (2.5 eq.) in dry THF was cooled to –30 °C under nitrogen, treated with *n*-BuLi (2.5 eq.), and stirred for 30 min to generate LDA.
A 10% suspension of the carboxylate **3a** in dry THF was cooled to –90 °C under nitrogen and treated with the freshly prepared LDA solution. Lithiation was completed by stirring at –50 °C for 90 min followed by addition of a 10% solution of the electrophile in dry THF at –90 °C. The reaction mixture was warmed to room temperature over a period of approx. 2 h and finally hydrolyzed with water. The organic layer was washed with diethyl ether, acidified with 2N HCl, and the precipitate isolated by filtration or by extraction with diethyl ether.

Lithiation of Amide 3b with *n*-BuLi and Introduction of Electrophiles (General Procedure B)

A 10%(w/v) solution of amide **3b** in dry THF was cooled to –90 °C under nitrogen and treated with *n*-BuLi (2.5 eq.). The solution was stirred for 2 h at –50 °C, and the electrophile (CO_2 gas or 2.2 eq. neat reagent) was added at –90 °C. The reaction mixture was slowly warmed to room temperature. The crude product was isolated after hydrolysis with 2N HCl by filtration of the precipitate or by extraction with EtOAc.

Esterification with DCC (General Procedure C)

4-Dimethylaminopyridine (0.1 eq.) and dry methanol (10 eq.) were added to a 5%(w/v) solution of the corresponding acid in dry CH_2Cl_2 followed by DCC (1 eq. per carboxylic acid group) in small portions. The resulting mixture was stirred at room temperature overnight. The urea formed was separated by filtration and washed with CH_2Cl_2, the organic layers were washed with 2N HCl, satd. $NaHCO_3$-soln., and water, dried over Na_2SO_4, and concentrated. Purification of the crude product was performed by flash column chromatography (FCC).

N-(1,1-Dimethylethyl)-thieno[2,3-d][1,2,3]thiadiazole-6-carboxamide (**3b**)

Acid **3a** (5.00 g, 26.85 mmol) was suspended in dry CH_2Cl_2 and refluxed with $SOCl_2$ (136 mL) until a clear solution was formed (approx. 4 h). After evaporation of the volatiles the acid chloride was dissolved in dry CH_2Cl_2 and added to a cooled solution of *tert*-butylamine (2 eq.) and dry NEt_3 (3 eq.) in CH_2Cl_2. The solution was stirred overnight, hydrolyzed with water, and extracted with CH_2Cl_2. The combined organic layers were washed with 2N HCl, satd. $NaHCO_3$-soln., and water, dried over Na_2SO_4, filtered, and concentrated. Recrystallization from MeOH gave 5.30 g (82%) of pure **3b** as colorless crystals (*m.p.* 148–151 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 1.48 (s, 9H), 6.1 (bs, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 28.8 (q), 52.3 (s), 127.9 (s), 133.9 (d), 146.6 (s), 159.6 (s), 162.2 (s).

$C_9H_{11}N_3OS_2$	Calcd.:	C 44.79	H 4.59	N 17.41
(241.33)	Found:	C 44.52	H 4.46	N 17.19.

5-Chloro-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid (**4a**) [3]

Acid **3a** (1.00g, 5.37 mmol) was converted according to general procedure A using hexachloroethane as electrophile to give 1.18 g (99%) of pure **4a** [3] as colorless crystals (*m.p.* 272–275 °C). – ^{13}C NMR (DMSO-d_6, 50 MHz), δ/ppm = 120.8 (s), 145.4 (s), 145.6 (s), 154.7 (s), 160.8 (s).

5-Iodo-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid (**4b**)

Acid **3a** (0.50 g, 2.67 mmol) was converted according to general procedure A using iodine as electrophile to give 0.50 g (60%) of pure **4b** as colorless crystals after recrystallization from EtOAc (*m.p.* 247–250 °C). – ^{13}C NMR (DMSO-d_6,

50 MHz), δ/ppm = 101.5 (s), 125.1 (s), 146.1 (s), 161.5 (s), 163.8 (s).

$C_5HIN_2O_2S_2$	Calcd.:	C 19.24	H 0.32	N 8.98
(312.11)	Found:	C 19.11	H 0.57	N 8.92.

5-Methylthio-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid (**4c**)

Acid **3a** (1.00 g, 5.37 mmol) was converted according to general procedure A using dimethyldisulfide as electrophile to give 0.92 g (74%) of pure **4c** as colorless crystals after trituration with EtOH (*m.p.* 195–198 °C). – ^{13}C NMR (DMSO-d_6, 50 MHz), δ/ppm = 17.6 (q), 115.4 (s), 148.0 (s), 156.3 (s), 162.3 (s), 164.4 (s).

$C_6H_4N_2O_2S_3$	Calcd.:	C 31.02	H 1.74	N 12.06
(232.31)	Found:	C 31.13	H 1.69	N 11.82.

5-Methyl-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid methylester **(4d)** [4]

Acid **3a** (1.00 g, 5.37 mmol) was converted according to general procedure A using methyliodide as electrophile followed by esterification according to general procedure C to give 0.25 g (20%) of pure **4d** [4] as colorless crystals after FCC (*m.p.* 101–104 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 2.95 (s, 3H), 4.00 (s, 3H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 17.3 (q), 52.3 (q), 117.9 (s), 147.6 (s), 157.8 (s), 160.1 (s), 161.6 (s).

5-Formyl-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid methylester (**4e**)

Acid **3a** (1.00 g, 5.37 mmol) was converted according to general procedure A using DMF as electrophile followed by esterification according to general procedure C to give 0.46 g (30%) of pure **4e** as beige crystals after FCC (*m.p.* 116–119 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 4.08 (s, 3H), 10.25 (s, 1H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 53.6 (q), 124.4 (s), 147.0 (s), 154.2 (s), 160.3 (s), 162.2 (s), 185.5 (d).

$C_7H_4N_2O_3S_2$	Calcd.:	C 36.84	H 1.77	N 12.27
(228.25)	Found:	C 36.64	H 1.85	N 12.18.

N-(1,1-Dimethylethyl)-5-formyl-thieno[2,3-d][1,2,3]thiadiazole-6-carboxamide (**4f**)

Amide **3b** (2.00 g, 8.28 mmol) was converted according to general procedure B using DMF as electrophile to give 1.09 g (50%) of pure **4f** as yellow crystals after FCC (*m.p.* 122–125 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 1.50 (s, 9H), 9.6 (bs, 1H), 9.91 (s, 1H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 28.5 (q), 52.1 (s), 131.7 (s), 142.6 (s), 150.2 (s), 157.3 (s), 160.8 (s), 185.6 (d).

$C_{10}H_{11}N_3O_2S_2$	Calcd.:	C 44.59	H 4.12	N 15.60
(269.34)	Found:	C 44.49	H 4.02	N 15.39.

Thieno[2,3-d][1,2,3]thiadiazole-5,6-dicarboxylic acid dimethylester (**4g**)

Acid **3a** (1.00 g, 5.37 mmol) was converted according to general procedure A using CO_2 gas as electrophile followed by esterification according to general procedure C to give 0.56 g (41%) of pure **4g** as yellow crystals after FCC (*m.p.* 106–108 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 3.97 (s, 3H), 3.98 (s, 3H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 53.1 (q), 53.6 (q), 122.6 (s), 144.5 (s), 146.6 (s), 160.3 (s), 160.4 (s), 160.6 (s).

$C_8H_6N_2O_4S_2$	Calcd.:	C 37.20	H 2.34	N 10.85
(258.27)	Found:	C 37.39	H 2.15	N 10.90.

6-[N-(1,1-Dimethylethyl)aminocarbonyl]-thieno[2,3-d][1,2,3]thiadiazole-5-carboxylic acid (**4h**)

Amide **3b** (0.50 g, 2.07 mmol) was converted according to general procedure B using CO_2 gas as electrophile to give 0.39 g (66%) of pure **4h** as yellow crystals after recrystallization from EtOAc (*m.p.* 226–227 °C). – ^{1}H NMR (DMSO-d_6, 200 MHz): δ/ppm = 1.45 (s, 9H), 5.5 (bs, 1H), 10.6 (bs, 1H). – ^{13}C NMR (DMSO-d_6, 50 MHz), δ/ppm = 28.0 (q), 51.0 (s), 130.7 (s), 141.2 (s), 148.5 (s), 157.7 (2 s), 164.6 (s).

$C_{10}H_{11}N_3O_3S_2$	Calcd.:	C 42.09	H 3.89	N 14.73
(285.35)	Found:	C 42.35	H 3.78	N 14.66.

5-Phenylmethylthio-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid methylester **(6a)**

Benzylthiol (1 eq.) was dissolved in dry DMF (10% solution) and deprotonated at 5°C with dry K_2CO_3 (2 eq). The cooled mixture was treated with **5** (200 mg, 0.85 mmol) in DMF (10% solution) and stirred overnight. After hydrolysis with water and extraction with EtOAc the combined organic layers were washed with 2N HCl, saturated $NaHCO_3$-soln, and water, dried over Na_2SO_4, and concentrated. FCC gave 220mg (80%) of pure **6a** as colorless crystals (*m.p.* 128–131 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 3.98 (s, 3H), 4.38 (s, 2H), 7.32–7.50 (m, 5H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 39.5 (t), 52.4 (q), 114.9 (s), 128.2, 128.8, and 129.1 (3 d), 133.8 (s), 147.2 (s), 157.3 (s), 161.5 (s), 161.9 (s).

$C_{13}H_{10}N_2O_2S_3$	Calcd.:	C 48.43	H 3.13	N 8.69
(322.43)	Found:	C 48.41	H 3.09	N 8.75.

5-(1-Pyrrolidinyl)-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid methylester (**6b**)

An ice cooled solution of pyrrolidine (2 eq.) in dry DMF (10% solution) was treated with **5** (200 mg, 0.85 mmol) in DMF (10% solution) and stirred for 2 h at room temperature. After hydrolysis with water and extraction with EtOAc the combined organic layers were washed with 1N HCl, satd. $NaHCO_3$-soln., and water, dried over Na_2SO_4, and concentrated. FCC gave 200 mg (87%) of pure **6b** as colorless crystals (*m.p.* 125–127 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 2.03 (t, J = 7 Hz, 4H), 3.55 (t, J = 7 Hz, 4H), 3.80 (s, 3H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 26.1 (t), 51.7 (q), 54.6 (t), 95.9 (s), 147.0 (s), 149.9 (s), 161.8 (s), 167.9 (s).

$C_{10}H_{11}N_3O_2S_2$	Calcd.:	C 44.59	H 4.12	N 15.60
(269.35)	Found:	C 44.66	H 3.96	N 15.57.

5-(4-Morpholinyl)-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid methylester (**6c**)

An ice cooled solution of morpholine (2 eq.) in dry DMF (10% solution) was treated with **5** (0.50 g, 2.13 mmol) in DMF (10% solution) and stirred for 2 h at room temperature. After hydrolysis with water and extraction with EtOAc the combined organic layers were washed with 1N HCl, satd. $NaHCO_3$-soln. and water, dried over Na_2SO_4, and concentrated. FCC gave 0.45 g (75%) of pure **6c** as colorless crystals (*m.p.* 120–122 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 3.53 (t, J = 7 Hz, 4H), 3.91 (s, 3H), 3.94 (t, J = 7 Hz, 4H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 52.1 (q), 52.9

(t), 66.1 (t), 101.9 (s), 148.3 (s), 148.6 (s), 161.0 (s), 172.3 (s).

$C_{10}H_{11}N_3O_3S_2$	Calcd.: C 42.09	H 3.89	N 14.73
(285.35)	Found: C 42.15	H 3.71	N 14.47.

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