ARTICLE

OBC
www.rsc.org/obc

Reaction of 5-halo-1,2,3-thiadiazoles with aliphatic diamines. Synthesis and intramolecular cyclization of bis(1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfides

Natalya N. Volkova,[a] Evgeniy V. Tarasov,[a] Mikhail I. Kodess,[b] Luc Van Meervelt,[c] Wim Dehaen *[c] and Vasiliy A. Bakulev *[a]

[a] *TOSLab, The Urals State Technical University, Ekaterinburg, Russia*

[b] *Institution of Organic Synthesis, The Urals Branch of Russian Academy of Sciences, Ekaterinburg, Russia*

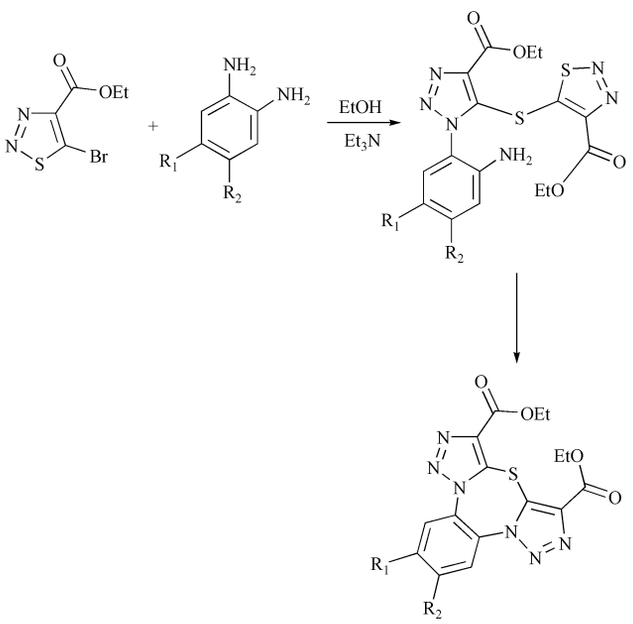
[c] *Department of Chemistry, University of Leuven, Heverlee (Leuven), B-3001, Belgium. E-mail: wim.dehaen@chem.kuleuven.ac.be*

Received 8th July 2003, Accepted 2nd September 2003
First published as an Advance Article on the web 13th October 2003

Bis[1,2,3]triazolo[1,5-*f*:5′,1′-*b*][1,3,6]thiadiazepine and [1,5-*g*:5′,1′-*b*][1,3,7]thiadiazocine ring systems have been synthesized from 5-halo-1,2,3-thiadiazoles and aliphatic diamines. We have found that the last step of the process is the cyclization of initially formed bis(1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfides. The structures of the intermediates and products were supported by different NMR spectroscopic methods (^{1}H coupled ^{13}C NMR, 2D HETCOR, HMBC and 1D INADEQUATE experiments) and mass spectrometry. Differences in the reaction pathway for aliphatic and less nucleophilic aromatic diamines were determined.

Introduction

In a previous paper[1] we reported the synthesis of 3,1,5-benzothiadiazepines from 5-halo-1,2,3-thiadiazoles and vicinal aromatic diamines which proceeded *via* sulfide as the intermediate (Scheme 1). In continuation of this work we were interested in studying the behavior of aliphatic diamines towards the same 1,2,3-thiadiazoles. In this paper we would like to report our results in this field.

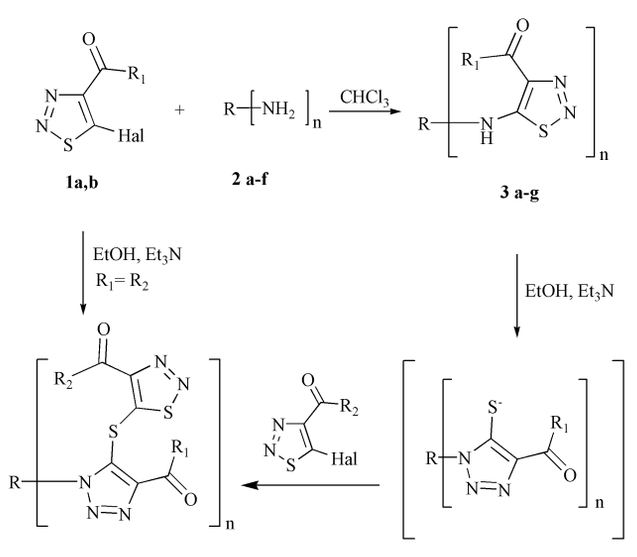


Scheme 1

Results

A. Reaction of 5-halo-1,2,3-thiadiazoles with aliphatic diamines

Our preliminary investigations[2] have shown that the reaction of ethyl 5-bromo-1,2,3-thiadiazole-4-carboxylate **1a** with ethylenediamine **2a** gives a 1,3,6-thiadiazepine derivative. Moreover, intermediates different to those found for *ortho*-phenylenediamines[1] were isolated. In order to study the mechanism, and to know the scope and limitations of this process, various aliphatic di- and polyamines **2a**–**f** were allowed to react with 1,2,3-thiadiazoles **1a**,**b**. Monoamines react with bromide **1a** in a sequence of reactions, including (1) halogen substitution, (2) Dimroth rearrangement and (3) heteroarylation of the resulting thiolate **4** with a second equivalent of **1a**. The same sequence is followed for the aliphatic di- and polyamines **2a**–**f** (Scheme 2, Table 1). In general, polar solvents and base promote all three processes.[3] Although the second amino group of *ortho*-phenylenediamine is not nucleophilic enough to substitute a halogen under these conditions, all amino groups of aliphatic amines **2a**–**f** are sufficiently reactive. As a result, the reaction readily



1a,b **2 a-f** **3 a-g**

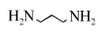
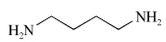
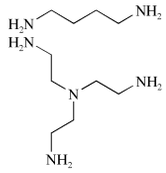
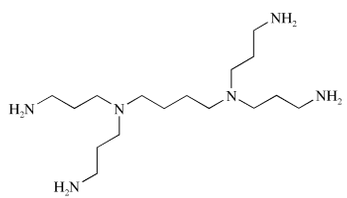
5 a-i **4**

1a $R_{1(2)}$ = OEt, Hal = Br; **b** $R_{1(2)}$ = NHMe, Hal = Cl
n = 2, 3, 4

Scheme 2

DOI: 10.1039/b307693h

Table 1

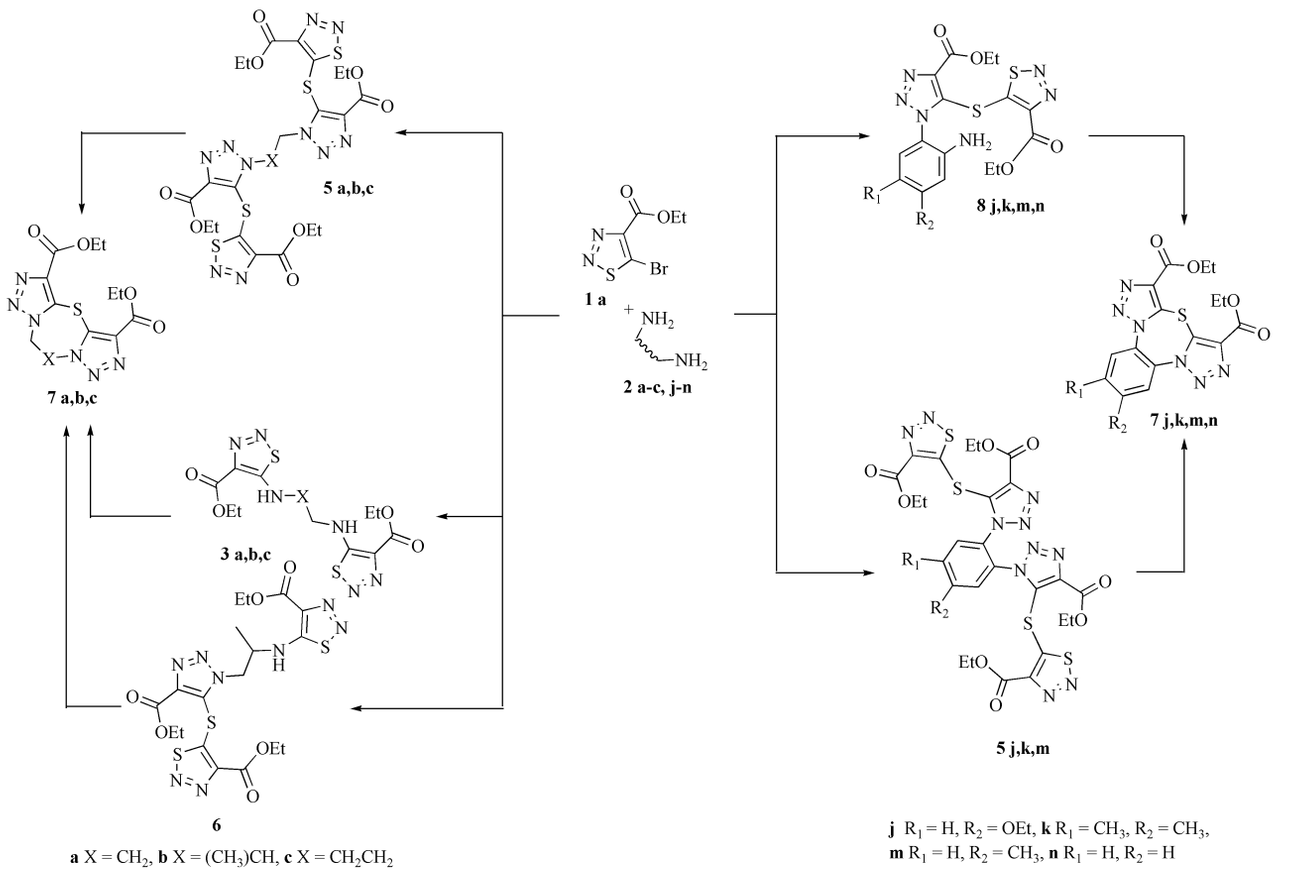
Amine **2**		**3**		**5**		
	R		R_1		R_1	R_2
a		a	OEt	a	OEt	OEt
		g	NHMe	g	NHMe	NHMe
				h	OEt	NHMe
				i	NHMe	OEt
b		b	OEt	b	OEt	OEt
c		c	OEt	c	OEt	OEt
d		d	OEt	d	OEt	OEt
e		e	OEt	e	OEt	OEt
f		f	OEt	f	OEt	OEt

affords multiply substituted products **3**, and further transformation yields symmetrical compounds **5** with a (1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfide moiety on each amino group. Thus, upon treatment of 5-halo-1,2,3-thiadiazoles **1a**,**b** with ethylenediamines **2b**–**d** in refluxing ethanol in the presence of triethylamine, bis-sulfides **5b**–**d**,**g** were obtained in good yields. The multistep process itself, is working simultaneously and independently on several reaction centers, providing a plethora of intermediates. Indeed, however many of them can be detected in the reaction of polyamine with 5-halo-1,2,3-thiadiazole, they all finally yield poly(1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfide **5** under the conditions mentioned above. On the other hand, changing the reaction conditions and the ratio of starting materials allows intermediate products to be obtained. Oligo(1,2,3-thiadiazolyl)amines **3a**–**f** can be obtained when a non polar solvent such as chloroform, is used. However, the rearrangement cannot be completely excluded because of the strong basic character of the oligoamine. This observation, and the necessity of obtaining a product that is substituted at all amine functions with a thiadiazole, prevents the use of excess amine. The latter is usual in the synthesis of 5-(*N*-alkyl)amino-1,2,3-thiadiazoles, in order to trap the hydrogen bromide generated.[3a] The use of triethylamine as acid scavenger promotes the Dimroth rearrangement. Therefore, the best yields were about 40–60%. As compounds of type **3** may undergo further transformation even in chloroform, the reaction mixture contains some thiolates of type **4** that are the products of the Dimroth rearrangement of one or both 1,2,3-thiadiazole rings. The thiolates were visible on TLC but were not isolated, as well as any other intermediates on the way to sulfide **5**. The reaction of **1a** with 1,2-diaminopropane **2b** in chloroform was the only case where we have isolated an intermediate product. When the reaction mixture was diluted with ethanol the [3+1] adduct **6** (in Scheme 3) was obtained in 12% yield. The formation of **6** does show that the 1,2,3-thiadiazole ring at C-1 of the 1,2-propane rearranges faster and this suggests that sterical hindrance reduces the rate of Dimroth rearrangement of 5-alkylamino-1,2,3-thiadiazoles.

Thus, the structure of the main product in the reaction of 5-halo-1,2,3-thiadiazole with oligoamines depends upon a variety of factors including reaction conditions (solvent, temperature, presence of base) and the ratio of the starting materials. The nature of the starting materials, which influences the comparative rates of substitution of bromothiadiazole **1a**, Dimroth rearrangement and substitution of bromothiadiazole **1a** with the resulting thiol also plays a significant role. Indeed, treatment of **1a** with ethylenediamine **2a** in refluxing ethanol without an additional base already afforded a significant amount of bis(sulfide) **5a**. On the other hand, 1,4-diaminobutane derivative **3d** requires stronger conditions for rearrangement. Compound **3d** does not rearrange in ethanol with 1 equivalent of triethylamine at room temperature. Only after heating, does further reaction to **5d** take place. In the case of tris(aminoethyl)amine **2e** and DAB-$(NH_2)_4$ **2f**, even after prolonged heating in ethanol–triethylamine, TLC control reveals remaining tris-substituted compounds **3e**,**f**. In order to convert all intermediates into final polysulfides **5e**,**f**, heating at 80–100 °C in DMF was necessary.

B. Unsymmetrically substituted sulfides

We were interested in preparing compounds **3a**,**g** in order to find a route to differently substituted (containing ester and amide groups at the same time) bis(sulfides) **5h**,**i**. Compound **3a** was easily obtained and upon heating at reflux in ethanol with methylamide **1b** afforded **5h**. However, when the methylamide **1b** was treated with ethylenediamine in chloroform we could not obtain the disubstituted product **3g**. Various reaction conditions (change of solvent, temperature, the sequence of reagents) resulted in almost the same mixture of products and in all experiments most of amide **1b** remained unconverted. Therefore, **1b** is reactive enough to be substituted by thiolates, but fails to react with amines. Traces of compound **3g** were detected in the ^{1}H NMR spectrum, displaying the characteristic signal for the ethylene protons at 3.5 ppm whereas the other material appeared to be bis(sulfide) **5g** and the products of single or double Dimroth rearrangement of **3g**. These experiments did not allow isolation of **3g** but bis(sulfide) **5i** could be obtained. Indeed, when the reaction mixture was separated from starting methylamide **1b** and refluxed in ethanol with ester **1a**, a mixture with an approximate 1 : 2 ratio of **5g** and **5i** was obtained. The latter was isolated by column chromatography. It



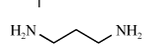
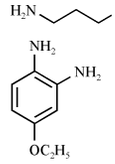
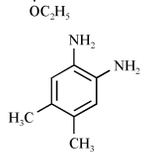
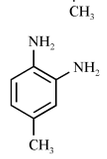
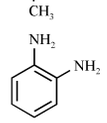
Scheme 3

is obvious that in this case the rates of the Dimroth rearrangement and the second substitution of halogen by thiol are much higher than that of the initial substitution of halogen.

C. Cyclization reactions

With the compounds **3**, **5** and **6** in hand, the possibility of their cyclization into seven-membered and larger rings was investigated. The results of this study are shown in Scheme 3 and Table 2. Firstly, we observed that **3a** was converted into bis[1,2,3]triazolo[1,5-*f*:5′,1′-*b*][1,3,6]thiadiazepine **7a** in a yield of about 20% on heating at reflux in ethanol in the presence of triethylamine. Later, it was found that sulfides **5a**–**c** and **6** afforded 1,3,6-thiadiazepines (1,3,7-thiadiazocines) **7a**–**c** under the same conditions. Compound **6** gave only 30% of cyclic product **7b** whereas bis(sulfides) **5a**–**c** surprisingly provided the best yields of thiadiazepines **7a**,**b** or 1,3,7-thiadiazocine **7c**. All attempts to obtain nine-membered rings by cyclization of bis(sulfide) **5d** were unsuccessful. It is evident that cyclization of **3** goes through a double Dimroth rearrangement followed by an intramolecular substitution of bis(thiolate) **4**. However, this process is not common in the literature. Examples of bis(thiol) cyclization to cyclic sulfides *via* acid-catalyzed dehydration[4] or desulfurization of initially formed disulfides with $P(NMe_2)_3$[5] were reported. Intramolecular cyclization of bis(sulfides) seems to be even more remarkable and also more promising for the preparation of 1,3,6-thiadiazepines. Ring formation of this type was described for compounds containing two methylsulfanyl groups either under demethylation conditions (sodium methanethiolate in DMF or lithium in liquid ammonia)[6] or by using pyridinium chloride.[7] In the case of our bis(sulfides) **5**, bis(1,2,3-thiadiazole-5-yl)disulfide **9** (Scheme 4) was detected after work-up indicating the easily oxidized 5-mercapto-1,2,3-thiadiazole to be one of the by-products. The other 1,2,3-thiadiazole ring probably decomposed after being removed from **5** with a nucleophile (hydroxide, triethylamine). It is also necessary to outline the role of the ester groups on both the 1,2,3-triazole and 1,2,3-thiadiazole rings in the formation of thiadiazepine **7**. Bis(sulfide) **5g**, when heated in DMF–Et_3N for several days was unchanged and compounds **5h**,**i** with combined ester/amide functions produce only sulfide bond cleavage

Table 2 Compounds **3**,**5**,**8**: yields (%)/melting points (°C)

Diamine		**3**	**5**	**8**
	**2a**	60/158	84/209	—
	**2b**	42/107	73/123	—
	**2c**	47/91	59/125	—
	**2j**	—	18/173	86/130
	**2k**	—	35/210	89/158[a]
	**2m**	[a]	76/190	87/140[b]
	**2n**	—	—	93/145[b]

[a] Was isolated when thiadiazepine **7m** was formed from **1a** and **2m**. [b] These compounds were characterized earlier.[1]

Table 3 ^{13}C NMR chemical shifts of synthesized compounds

Compound	Triazole							Thiadiazole-S				Thiadiazole-NH			
	C5	C4	CO	CH_2	CH_3	NCH_2	X	C5	C4	CO	CH_2	CH_3	C5	C4	CO	CH_2	CH_3
3a						50.13							171.12	132.39	163.60	61.62	14.39
4a	131.95	141.91	159.04	62.29	14.04	47.69		159.68	147.26	160.54	62.93	14.31					
4b	132.02	141.81	158.96	62.25	13.97	51.84	54.76 CH	159.99	147.18	160.53	62.86	14.25					
	131.40[a]	141.60	158.88		13.95		19.94CH_3	159.68	147.09	160.48							
4c	131.06	141.94	159.13	62.18	14.01	46.05	29.35CH_2	160.29	147.12	160.53	62.88	14.26					
5	132.15	141.72	159.15	62.32	14.06	52.60	58.65 CH	159.87	147.14	160.61	62.93	14.33	169.63	132.43	163.50	61.74	14.33
							18.57CH_3										
6a	130.20	138.04	159.89	61.99	14.21	49.33											
6b	130.6	138.5	160.2	62.1	14.3	53.0	56.2 CH										
	129.4[a]	137.4	159.8	62.0			17.8 CH_3										
6c	131.3	138.5	160.2	62.1	14.3	44.9	27.7 CH_2										
11	124.60	134.72				47.78											

[a] Is determined as C5 of triazole attached to $-CH(CH_3)-$.

Scheme 4

products, with virtually no cyclization. Thus, ester functions are necessary at the heterocyclic ring for the intra- and intermolecular nucleophilic aromatic substitutions to occur.

D. Structural investigations

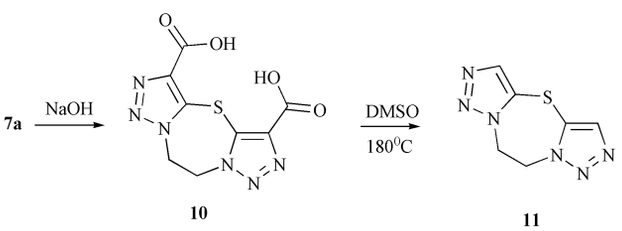
The structures of dithiadiazolylidiamines **3**, bis(sulfides) **5**, adduct **6** and 1,3,6-thiadiazepines **7** were completely supported by NMR spectroscopy. ^{13}C NMR chemical shifts are summarized in Table 3. We can clearly distinguish the signals due to the 1,2,3-triazole or the 1,2,3-thiadiazole rings, that are either connected through S or NH, and their substituents. The ^{1}H NMR spectra of these compounds are rather simple, especially for symmetrical structures and contain characteristic signals for the methylene protons at 3.64 ppm for compounds **3**, and at 4.6–5.2 ppm for methylene groups attached to the triazole nitrogen (**5**,**6**,**7**). Signals of ester groups on a thiadiazole ring occupy a downfield position (4.58 and 1.52 ppm for CH_2 and CH_3, respectively) as compared with the corresponding resonances for triazole ethoxycarbonyl groups at 4.37 and 1.33 ppm. The signals in the ^{1}H and ^{13}C NMR spectra were assigned based on the analysis of HETCOR and HMBC data. 2D experiments were made to reveal the $^{1}J_{CH}$ connectivities, but in the case of bis(sulfides) **5**, due to the lack of protons these data were not sufficient to make a complete assignment. Therefore, a 1D INADEQUATE experiment was performed for compounds **5b** and **5c** because of their high solubility, and the carbon–carbon coupling constants were determined. With the help of this information we were able to assign these groups of signals to either the 1,2,3-triazole or 1,2,3-thiadiazole ring. However it was still impossible to establish the difference between similar heterocyclic carbons in unsymmetrical bis(sulfide) **5b**. Spin–spin coupling constants between ^{13}C nuclei for triazole and thiadiazole rings which are of interest and are not readily available in the literature[8] are presented in Table 4.

Mass spectra of bis(sulfides) **5** were taken using the electrospray technique. It is worth knowing that the EI-MS technique, though not allowing us to obtain molecular ions of bis(sulfides) **5a**–**c**, showed the formation of corresponding heterocycles **7** during gas phase fragmentation. The most intensive peaks of the electron impact MS of **5** corresponded to the molecular ion following fragmentation of thiadiazepine(azocine). Interestingly, the fragmentation pattern of **5d** does not contain peaks corresponding to the appropriate thiadiazonine.

Table 4 ^{13}C–^{13}C coupling constants for compounds **4b**,**c** measured in 1D INADEQUATE experiment

Compound	Triazole		Thiadiazole	
	$^1J_{C5-C4}$	$^1J_{C4-CO}$	$^1J_{C5-C4}$	$^1J_{C4-CO}$
4b	73.6	95.2	90.2	66.3
	73.9	94.7	90.7	66.9
4c	73.4	95.0	91.0	66.8

The parent heterocyclic system 9,10-dihydrobis[1,2,3]triazolo[1,5-*f*:5′,1′-*b*][1,3,6]thiadiazepine **11** was obtained from ester **7a** by saponification followed by decarboxylation of diacid **10** (Scheme 5). Compound **11** was subjected to crystallographic analysis. The compound shows no molecular symmetry. The thiadiazepine ring occurs in a boat conformation with atoms S1 and C4 at the opposite side of the fused triazole rings with respect to the best plane through the seven-membered ring. This best plane makes an angle of 26.1(1)° and 13.0(1)° with the best planes through the five-membered rings. Both triazole rings make an angle of 49.0(1)° to each other. (Fig. 1).



10 **11**

Scheme 5

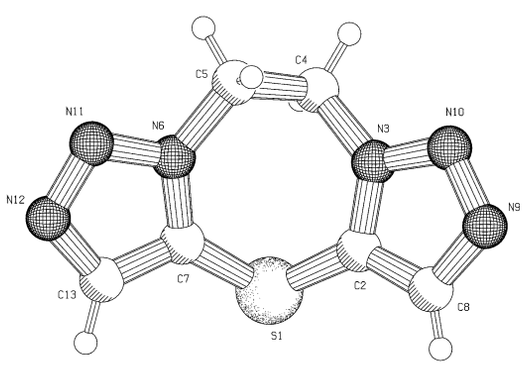


Fig. 1 Molecular structure of parent heterocycle **11**.

E. Reactions with aromatic diamines

For aromatic diamines, the main route to 3,1,5-benzothiadiazepine **7** proceeds *via* sulfide **8**, but for the reaction of 5-bromo-1,2,3-thiadiazole **1a** with phenylenediamines containing electron rich functions **2j**–**m**, the same pathway as for the aliphatic oligoamines was observed. In this case, bis(sulfides) of type **5** were detected among the intermediates. It was found that in ethanol solution in the presence of triethylamine at room temperature, with a 1 : 4 ratio of starting compounds **2j**–**m** : **1a**, both amino groups were substituted and products of type **5j**–**m** were formed. The same conditions for **2n** produce only sulfide **8n**. Analogously to compounds **5a**–**c**, the EI-MS spectra of bis(sulfides) **5j**–**m** revealed the transformation into thiadiazepines **7j**–**m** in the gas phase. At the same time, treatment of initially isolated 5-amino-1,2,3-thiadiazole **12j**–**m** with 1 eq. bromoester **1a** in basic media at room temperature afforded sulfides **8j**–**m** in good yields. When thiadiazepines **7** were formed in refluxing ethanol–triethylamine, both compounds **5** and **8** were detected as intermediates in the reaction mixture by means of TLC analysis, although both of them disappeared to the extent that the thiadiazepine ring was formed. We may argue that the reaction may simultaneously proceed *via* two different intermediates **5** and **8**. As proof of this supposition, isolated **5m** was transformed into **7m** on refluxing in ethanol with Et_3N in 79% yield. Unexpectedly, 4-methylphenylenediamine **2m** undergoes nucleophilic substitution of both amino groups more readily then diamines **2k** and **2j**. So far, we are not able to explain this fact. While diamines **2j**,**k** produce only 18–35% of bis(sulfides) **5j**,**k**, and the other products were found to be monosulfides **8** and even 5-arylamino-1,2,3-thiadiazoles **12**, the yield of **5m** is remarkably high. The formation of bis(sulfide) **5m** occurred even when starting materials **1a** : **2m** were combined in a 2 : 1 ratio. In this case, when the reaction is over, one can see by TLC control the unconverted diamine **2m** along with **5m**. Moreover, when thiadiazepine **7m** was formed from **1a** and **2m**, bis(1,2,3-thiadiazolyl) substituted phenylenediamine **3m** was unexpectedly obtained along with disulfide **9** as a by-product. Compound **3m** could be generated in this reaction either by direct heteroarylation of phenylenediamine or by transformation of sulfide **8m** for which the transposition of thiadiazole ring from sulfur to amino group (Smiles-type rearrangement), followed by Dimroth rearrangement could be supposed. We tried to obtain bis(substituted) **3m** by heteroarylation of phenylenediamine **2m** but the only product was the monosubstituted compound **12m**. On the contrary, treatment of sulfide **8m** with NaH in dimethyl formamide easily afforded **3m** in more than 70% yield. The analogous product **3n** was obtained from sulfide **8n**. Compounds **3m**,**n** also afford cyclization products **7m**,**n** in a yield of 25–30%.

Conclusion

In conclusion, various vicinal diamines react with 5-halo-1,2,3-thiadiazoles to form the bis[1,2,3]triazolo[1,5-b:5′,1′-f][1,3,6]-thiadiazepine system **7**. The mechanism of the transformation depends upon the reactivity of the diamine. This was proved by isolation of the intermediates shown in Table 2. Thus, for aromatic diamines sulfide **8** is initially formed, and electron-rich phenylenediamines also produce bis(sulfides) **5**. Highly reactive aliphatic diamines in polar basic media gave compounds **5** exclusively, while the use of nonpolar solvents afforded bis(substituted) products **3**. The intermediates **3**,**5**,**8** underwent transformation into seven (or eight)-membered rings.

Experimental

Materials and methods

^1H and ^{13}C NMR spectra were recorded respectively on a Bruker WM-250, Bruker WM-300 and Bruker DRX-400 in either $(CD_3)_2SO$ or $CDCl_3$ solutions. 2D NMR experiments were carried out using standard pulse sequences from the Bruker NMR Suite 2.6 software. ESI-MS spectra were scanned on a Micromass Quatro II (infusion of 50 ìl MeOH–CH_2Cl_2 – NH_4OAc(0.1 M in MeOH) with Harvard pump, model 11), electron impact mass spectra were obtained on a Varian MAT 311 machine. Products were analyzed by TLC on DC-Plastikfolien Kieselgel 60 F 254 plates. Melting points were taken in open capillaries and are uncorrected. Commercial samples of amines **2a**–**f**,**k**–**n** were used. 4-Ethoxyphenylenediamine **2j** was obtained by reduction of 2-nitro-4-ethoxyaniline with hydrazine over palladium.

Diethyl 5,5′-[ethane-1,2-diyldi(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3a. A solution of bromoester **1a** (0.5 g, 2.1 mmol) and 0.75 equivalents of ethylenediamine **2a** (0.1 g) in chloroform (5 mL) was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in ethanol acidified with hydrochloric acid, and the precipitated product was filtered off and crystallized from ethanol yielding 0.47 g (60%) of white crystals, mp 148 °C. ^1H NMR δ_H ($CDCl_3$, 400 MHz): 1.44 (6H,

t, J = 7.2 Hz, 2CH_3), 3.64 (4H, m, CH_2CH_2), 4.45 (4H, q, J = 7.2 Hz, 2OCH_2), 8.06 (2H, t, 2NH). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 14.39 (qt, J = 127.4, 2.7 Hz, 2CH_3), 50.13 (tdt, J = 139.9, 3.2, 3.2 Hz, CH_2CH_2), 61.62 (tq, J = 148.3, 4.4 Hz, 2OCH_2), 132.39 (d, J = 1.5 Hz, C4-thiadiazole), 163.60 (t, J = 3.4 Hz, CO), 171.12 (td, J = 4.6, 2.6 Hz, C5-thiadiazole). EIMS m/z (rel. int.): 372 (M^+,9), 190 (31). Anal. Calcd for $C_{12}H_{16}N_6O_4S_2$: C, 38.70; H, 4.33; N, 22.57; S, 17.22. Found C, 38.73; H, 4.30; N, 22.53; S, 17.29%.

Diethyl 5,5′-[propane-1,2-diyldi(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3b. A solution of bromoester **1a** (0.5 g, 2.1 mmol) and 0.75 equivalents of 1,2-propylenediamine **2b** (0.12 g) in chloroform (5 mL) was refluxed for 3 hours. The solvent was evaporated and the crude product was purified by column chromatography using chloroform as the eluent. Yield 42%, mp 107 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.42–1.48 (9H, m, 3CH_3), 3.50 (3H, m, CH + CH_2), 4.45 (4H, m, 2OCH_2), 7.86 (1H, d, J = 7.2 Hz, N*H*CH), 8.07 (1H, t, J = 5.2 Hz, N*H*CH_2). EIMS m/z (rel. int.): 387 (MH^+,100). Anal. Calcd for $C_{13}H_{18}N_6O_4S_2$: C, 40.40; H, 4.69; N, 21.75. Found C, 40.37; H, 4.70; N, 21.80%.

Diethyl 5,5′-[propane-1,3-diyldi(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3c. Prepared from **1a** and **2c** as described for **3b**. Yield 47%, mp 91 °C. ^{1}H NMR δ_H ($CDCl_3$, 250 MHz): 1.45 (6H, t, J = 7.1 Hz, 2CH_3), 2.15 (2H, m, J = 6.7 Hz, CH_2 centr.), 3.43 (4H, m, J = 6.1 Hz, 2CH_2), 4.46 (4H, q, J = 7.1 Hz, 2CH_2 ester), 7.93 (2H, m, 2NH). EIMS m/z (rel. int.): 386 (M^+, 4), 169 (100). Anal. Calcd for $C_{13}H_{18}N_6O_4S_2$: C, 40.40; H, 4.69; N, 21.75. Found C, 40.33; H, 4.68; N, 21.72%.

Diethyl 5,5′-[butane-1,4-diyldi(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3d. Prepared from **1a** and **2d** as described for **3a**. Yield 53%, mp 106 °C. ^{1}H NMR δ_H ($CDCl_3$, 250 MHz): 1.84 (4H, m, 2CH_2), 3.34 (4H, m, 2NHCH_2), 4.45 (4H, q, J = 7.0 Hz, 2OCH_2), 7.88 (2H, m, 2NH).11.45 (6H, t, J = 7.0 Hz, 2CH_3), EIMS m/z (rel. int.): 400 (M^+, 0.8), 203 (9), 126 (20). Anal. Calcd for $C_{14}H_{20}N_6O_4S_2$: C, 41.99; H, 5.03; N, 20.98. Found C, 42.05; H, 5.09; N, 20.89%.

***N′*-4-Ethoxycarbonyl-1,2,3-thiadiazol-5-yl-*N*,*N*-bis[2-(4-ethoxycarbonyl-1,2,3-thiadiazol-5-ylamino)ethyl]ethane-1,2-diamine 3e.** To a solution of **1a** (1 g, 4.22 mmol) in ethanol (50 mL), tris(2-aminoethyl)amine **2e** (0.21 g, 1.40 mmol) was added and the reaction mixture was refluxed overnight. After cooling, the precipitate was filtered off and crystallized from ethanol. Yield 44%, mp 144 °C. ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 1.35 (9H, t, J = 7.3, 3CH_3), 2.93 (6H, m, 3NCH_2), 3.32 (6H, m, 3$NHCH_2$), 4.28 (6H, q, J = 7.3 Hz, 3OCH_2), 8.16 (3H, m, 3NH). ESI-MS 615 (MH^+). Anal. Calcd for $C_{21}H_{30}N_{10}S_3O_6$: C, 41.03; H, 4.92; N, 22.79; S, 15.65. Found C, 40.97; H, 4.90; N, 22.83; S, 15.56%.

Tetra-[4-ethoxycarbonyl-([1,2,3]-thiadiazol-5-yl)]-DAB-Am-4 3f. To a solution of **1a** (1 g, 4.22 mmol) in 50 mL of ethanol DAB-(NH_2)$_4$, **2f** (0.44 g, 1.05 mmol, 75% reagent) was added and the reaction mixture was refluxed for 2 days. The solvent was removed, chloroform added and precipitate was filtered off and dried in a vacuum over P_2O_5. Yield 25%, mp 188 °C. ^{1}H NMR δ_H (DMSO-D_6, 400 MHz): 1.33 (12H, t, J = 7.1 Hz, 4CH_3), 1.65 (4H, m, $NCH_2CH_2CH_2CH_2N$), 2.00 (8H, m, $NHCH_2CH_2CH_2N$), 3.11 (12H, m, 6NCH_2), 3.35 (8H, m, 4$NHCH_2$), 4.35 (8H, q, J = 7.1 Hz, 4OCH_2), 8.44 (4H, t, J = 5.4 Hz, 4NH). ^{13}C NMR δ_C (DMSO-D_6, 100 MHz): 14.28 (CH_3), 21.90, 48.98, 49.51, 51.20, 60.44 (OCH_2), 130.96 (C4-thiadiazole), 162.21 (CO), 170.53 (C5-thiadiazole). Anal. Calcd for $C_{36}H_{56}N_{14}S_4O_8$: C, 45.94; H, 6.00; N, 20.83. Found C, 45.81; H, 6.07; N, 20.69%.

Diethyl 5,5′-[(4-methyl-1,2-phenylene)di(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3m. Sulfide **8m** (0.15g, 0.34 mmol) was dissolved in dry DMF under stirring and cooling on the ice bath. Sodium hydride (0.1 g, 60% dispersion in mineral oil) was added and reaction was stirred for 1 hour at room temperature and quenched with water. Upon acidification, the product precipitated and was filtered off and washed with ethanol. Yield 74%, mp 138 °C. ^{1}H NMR δ_H (DMSO-D_6+CCl_4, 250 MHz): 1.40 (3H, t, J = 7.0 Hz, CH_3), 1.41 (3H, t, J = 7.0 Hz, CH_3), 2.41 (3H, s, CH_3), 4.42 (2H, q, J = 7.0 Hz, CH_2), 4.43 (2H, q, J = 7.0 Hz, CH_2), 7.21 (1H, d, J = 7.6 Hz, C3H), 7.34 (1H, s, C1H), 7.43 (1H, d, J = 8.2 Hz, C4H), 9.93 (1H, s, NH), 10.04 (1H, s, NH). EIMS m/z (rel. int.): 434 (M^+,20). Anal. Calcd for $C_{17}H_{18}N_6S_2O_4$: C, 46.99; H, 4.18; N, 19.34. Found C, 46.91; H, 4.22; N, 19.30%.

Diethyl 5,5′-[(1,2-phenylene)di(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3n. Prepared from **8n** as described for **3m**. Yield 79%, mp 132 °C. ^{1}H NMR δ_H (DMSO-D_6+CCl_4, 250 MHz): 1.41 (6H, t, J = 7.0 Hz, 2CH_3), 4.43 (4H, q, J = 7.0 Hz, 2CH_2), 7.41–7.47 (2H, m, CH-arom.), 7.53–7.59 (2H, m, CH-arom), 10.07 (2H, s, 2NH). EIMS m/z (rel. int.): 420(M^+,31). Anal. Calcd for $C_{16}H_{16}N_6S_2O_4$: C, 45.71; H, 3.84; N, 19.99. Found C, 45.76; H, 3.81; N, 20.03%.

5,5′-{Ethane-1,2-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4- ethoxycarbonyl-1,2,3-thiadiazole) 5a. To a solution of bromoester **1a** (0.5 g, 2.1 mmol) and ethylenediamine **2a** (0.03 g, 0.52 mmol) in ethanol (30 mL), triethylamine (0.3 mL, 2.1 mmol) was added and the mixture was refluxed for 5 hours. The product began to precipitate from the boiling solution and after cooling was filtered off and crystallized from ethanol yielding 0.30 g (84%) of white crystals, mp 209 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.33 (6H, t, J = 7.1 Hz, 2CH_3-triaz.), 1.51 (6H, t, J = 7.1 Hz, 2CH_3-thiadiaz.), 4.38 (4H, q, J = 7.1 Hz, 2OCH_2-triaz.), 4.57 (4H, q, J = 7.1 Hz, 2OCH_2-thiadiaz.), 5.18 (4H, s, CH_2CH_2). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 14.04 (qt, J = 127.6, 2.7 Hz, 2CH_3-triaz.), 14.31 (qt, J = 127.6, 2.7 Hz, 2CH_3-thiadiaz.), 47.69 (tt, J = 146.8, 3.6 Hz, CH_2CH_2), 62.29 (tq, J = 148.8, 4.4 Hz, 2OCH_2-triaz.), 62.93 (tq, J = 149.0, 4.4 Hz, 2OCH_2-thiadiaz.), 131.95 (t, J = 1.1 Hz, C5-triaz.), 141.91 (s, C4-triaz.), 147.26 (s, C4-thiadiaz.), 159.04 (t, J = 3.2 Hz, CO-triaz.), 159.68 (s, C5-thiadiaz.), 160.54 (t, J 3.2 Hz, CO-thiadiaz.). ESI-MS 685 (MH^+). EIMS m/z (rel. int.): 529(1), 370(28), 339(38), 240(50), 199(32), 157(60), 114(55), 85(100). Anal. Calcd for $C_{22}H_{24}N_{10}O_8S_4$: C, 38.59; H, 3.53; N, 20.46; S, 18.73. Found C, 38.62; H, 3.56; N, 20.74; S, 18.51%.

5,5′-{Propane-1,2-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5b. Prepared from **1a** and **2b** as described for **5a**. Yield 73%, mp 123 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.315 (3H, t, J = 7.1 Hz, CH_3-triaz.), 1.317 (3H, t, J = 7.1 Hz, CH_3-triaz.), 1.519 (3H, t, J = 7.1 Hz, CH_3-thiadiaz.), 1.521 (3H, t, J = 7.1 Hz, CH_3-thiadiaz.), 1.77 (3H, d, J = 6.8 Hz, CH_3), 4.366 (2H, q, J = 7.1 Hz, OCH_2-triaz.), 4.371 (2H, q, J = 7.1 Hz, OCH_2-triaz.), 4.581 (2H, q, J = 7.1 Hz, OCH_2-thiadiaz.), 4.585 (2H, q, J = 7.1 Hz, OCH_2-thiadiaz.), 4.88, 5.43 (2H, AB-syst., J = 14.3, 9.9, 4.0 Hz, CH_2), 5.77 (1H, dqd, J = 9.9, 6.8, 4.0 Hz, CH). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 13.95 (qt, J = 127.6, 3.6 Hz, CH_3-triaz.), 13.97 (qt, J = 127.5, 2.6 CH_3-triaz.), 14.25 (qt J = 127.6, 2.7 Hz, 2CH_3-thiadiaz.), 19.94 (qdt, J = 130.5, 3.9, 2.0 Hz, CH_3), 51.84 (tt, J = 145.7, 5.9Hz, CH_2CH), 54.76 (dm, J = 145.5 Hz, CH), 62.20 (tq, J = 148.6, 4.9 Hz, OCH_2-triaz.), 62.25 (tq, J = 149.0, 4.6 Hz, OCH_2-triaz.), 62.86 (tq J = 149.1, 4.5 Hz, 2OCH_2-thiadiaz.), 131.40 (d, J = 1.8 Hz, *C5*-triaz.CH), 132.02 (t, J = 2.1 Hz, *C5*-triaz.CH_2), 141.60 (s, C4-triaz.), 141.81 (s, C4-triaz.), 147.09 (s, C4-thiadiaz.), 147.18 (s, C4-thiadiaz.), 158.88 (t, J = 3.2 Hz, CO-triaz.), 158.96 (t,

J = 3.2 Hz, CO-triaz.), 159.68 (s, C5-thiadiaz.), 159.99 (s, C5-thiadiaz.), 160.48 (t, J = 3.4 Hz, CO-thiadiaz.), 160.53 (t, J = 3.2 Hz, CO-thiadiaz.). ESI-MS 699 (MH^+). EIMS *m/z* (rel. int.): 514(1), 384(18), 352(12), 318(14), 235(43), 157(58), 129(37), 116(45), 85(100). Anal. Calcd for $C_{23}H_{26}N_{10}O_8S_4$: C, 39.53; H, 3.75; N, 20.04. Found C, 39.59; H, 3.78; N, 20.01%.

5,5′-{Propane-1,3-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5c. Prepared from **1a** and **2c** as described for **5a**. Yield 59%, mp 125 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.33 (6H, t, J = 7.1 Hz, $2CH_3$-triaz.), 1.52 (6H, t, J = 7.1 Hz, $2CH_3$-thiadiaz.), 2.66 (2H, quintet, J = 6.7 Hz, $CH_2CH_2CH_2$), 4.39 (4H, q, J = 7.1 Hz, $2OCH_2$-triaz.), 4.58 (4H, q, J = 7.1 Hz, $2OCH_2$-thiadiaz.), 4.64 (4H, t, J = 6.7 Hz, $CH_2CH_2CH_2$). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 14.01 (qt, J = 127.5, 2.6 Hz, $2CH_3$-triaz.), 14.26 (qt, J = 127.6, 2.7 Hz, $2CH_3$-thiadiaz.), 29.35 (tq, J = 132.3, 3.0 Hz, $CH_2CH_2CH_2$), 46.05 (tt, J = 143.9, 4.5 Hz, $CH_2CH_2CH_2$), 62.18 (tq, J = 148.7, 4.4 Hz, OCH_2-triaz.), 62.88 (tq, J = 149.1, 4.4 Hz, OCH_2-thiadiaz.), 131.06 (t, J = 2.4 Hz, C5-triaz.), 141.94 (s, C4-triaz.), 147.12 (s, C4-thiadiaz.), 159.13 (t, J = 3.4 Hz, CO-triaz.), 160.29 (s, C5-thiadiaz.), 160.53 (t, J = 3.2 Hz, CO-thiadiaz.). ESI-MS 699 (MH^+). EIMS *m/z* (rel. int.): 384(18), 352(10), 318(18), 245(40), 218(33), 169(44), 130(30), 116(36), 85(100). Anal. Calcd for $C_{23}H_{26}N_{10}O_8S_4$: C, 39.53; H, 3.75; N, 20.04. Found C, 39.54; H, 3.71; N, 20.29%.

5,5′-{Butane-1,4-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5d. Prepared from **1a** and **2d** as described for **5a**. Yield 91%, mp 178 °C. ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 1.34 (6H, t, J = 7.1 Hz, $2CH_3$), 1.51 (6H, t, J = 7.1 Hz, $2CH_3$), 1.97 (4H, m, $2CH_2$), 4.40 (4H, q, J = 7.1 Hz, $2COCH_2$), 4.54 (4H, m, $2NCH_2$), 4.58 (4H, q, J = 7.1 Hz, $2COCH_2$). ESI-MS 713 (MH^+). EIMS *m/z* (rel. int.): 456(2), 428(3), 395(9), 256(100), 182(19), 70(17), 55(67). Anal. Calcd for $C_{24}H_{28}N_{10}O_8S_4$: C, 40.44; H, 3.96; N, 19.65; S, 17.99. Found C, 40.38; H, 4.00; N, 17.93; S, 17.38%.

***N,N′,N″*-Tris{4-ethoxycarbonyl-5-[(4-ethoxycarbonyl-1,2,3-thiadiazol-5-yl)sulfanyl]-1*H*-1,2,3-triazol-1-yl}aminoethylamine 5e.** To a solution of bromoester **1a** (1.0 g, 4.2 mmol) and tris-(2-aminoethyl)amine **2e** (0.11 g, 0.70 mmol) in DMF (15 mL), triethylamine (0.6 mL, 4.2 mmol) was added and the mixture was heated at 90 °C for 2 days. Then, the mixture was diluted with water, the product filtered off and purified by column chromatography with CH_2Cl_2–ethanol 10 : 1 yielding 0.58 g (76%) of sulfide **5e**, mp 114 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.30 (9H, m, $3CH_3$-triaz.), 1.48 (9H, m, $3CH_3$-thiadiaz.), 3.14 (6H, m, $3NCH_2$), 4.37 (6H, m, $3OCH_2$-triaz.), 4.52 (12H, m, $3OCH_2$-thiadiaz. + 3N-triaz.-CH_2). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 13.98 (CH_3-triaz.), 14.24 (CH_3-thiadiaz.), 46.52 (NCH_2CH_2), 53.22 (NCH_2CH_2), 62.05 (OCH_2-triaz.), 62.83 (OCH_2-thiadiaz.), 131.31 (C5-triaz.), 141.44 (C4-triaz.), 147.05 (C4-thiadiaz.), 159.33 (CO-triaz.), 160.57 (CO-thiadiaz. + C5-thiadiaz.). ESI-MS 1083 (M^+). Anal. Calcd for $C_{36}H_{42}N_{16}O_{12}S_6$: C, 39.92; H, 3.91; N, 20.69. Found C, 39.89; H, 3.90; N, 20.71%.

DAB-dendr-([4-ethoxycarbonyl-1,2,3-thiadiazol-5-yl]-NH)$_4$ 5f. Prepared from **1a** and **2f** as described for **5e**. Yield 61%, mp 102 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.30 (12H, m, $4CH_3$-triaz.), 1.39 (4H, m, $NCH_2CH_2CH_2CH_2N$), 1.49 (12H, t, J = 7.1 Hz, $4CH_3$-thiadiaz.), 2.02 (8H, m, $NHCH_2CH_2CH_2N$), 2.44 (12H, m, $6NCH_2$), 4.36 (8H, m, $4OCH_2$-triaz.), 4.53 (8H, q, J = 7.1 Hz, $4OCH_2$-thiadiaz.), 4.62 (8H, m, 4N-triaz.-CH_2). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 14.07 (CH_3-triaz.), 14.32 (CH_3-thiadiaz.), 24.40, 27.88, 47.55, 50.48, 53.44, 62.07 (OCH_2-triaz.), 62.82 (OCH_2-thiadiaz.), 130.83 (C5-triaz.), 141.59 (C4-triaz.), 146.88 (C4-thiadiaz.), 159.38 (CO-triaz.), 160.68 (CO-thiadiaz. + C5-thiadiaz.). ESI-MS 1566 (MH^+). Anal. Calcd for $C_{56}H_{72}N_{22}O_{16}S_8$: C, 42.96; H, 4.63; N, 19.68. Found C, 42.76; H, 4.39; N, 19.73%.

5,5′-{Ethane-1,2-diylbis[(4-(*N*-methylcarbamoyl)-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-(*N*-methylcarbamoyl)-1,2,3-thiadiazole) 5g. Prepared from **1b** and **2a** as described for **5a**. Yield 45%, mp 236 °C. ^{1}H NMR δ_H (DMSO-D_6 + CCl_4, 250 MHz): 2.76 (6H, d, J = 4.0 Hz, $2CH_3$), 2.91 (6H, d, J = 4.0 Hz, $2CH_3$), 5.04 (4H, s, $2CH_2$), 8.54 (2H, q, J = 4.3 Hz, 2NH), 8.94 (2H, q, J = 4.0 Hz, 2NH). ESI-MS 625 (M^+). EIMS *m/z* (rel. int.): 300(1), 288(2), 231(2), 203(22), 174(6), 146(9), 114(6), 98(7), 86(24), 74(14), 58(100). Anal. Calcd for $C_{18}H_{20}N_{14}O_4S_4$: C, 34.61; H, 3.23; N, 31.39. Found C, 36.65; H, 3.20; N, 31.42%.

5,5′-{Ethane-1,2-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-(*N*-methylcarbamoyl)-1,2,3-thiadiazole) 5h. To a solution of **3a** (0.25 g, 0.67 mmol) and 5-chloro-1,2,3-thiadiazole **1b** (0.24 g, 1.30 mmol) in ethanol (30 mL), triethylamine (0.1 mL, 0.70 mmol) was added and the mixture was heated at reflux for 5 hours. After cooling, the product was filtered off and crystallized from ethanol yielding 0.22 g (50%) of **5h**, mp 216 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.32 (6H, t, J = 7.2 Hz, $2CH_3$), 3.10 (6H, d, J = 5.1 Hz, $2NHCH_3$), 4.38 (4H, q, J = 7.2 Hz, $2OCH_2$), 5.10 (4H, s, $2CH_2$), 7.41 (2H, q, J = 5.1 Hz, 2NH). ESI-MS 655 (M^+). EIMS *m/z* (rel. int.): 402 (1), 370 (22), 338 (27), 240 (22), 199 (20), 147 (42). Anal. Calcd for $C_{20}H_{22}N_{12}O_6S_4$: C, 36.69; H, 3.39; N, 25.67. Found C, 36.74; H, 3.35; N, 25.65%.

5,5′-{Ethane-1,2-diylbis[(4-(*N*-methylcarbamoyl)-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5i. A solution of chloroamide **1b** (1.0 g, 5.6 mmol) and ethylenediamine **2a** (0.25 g, 4.2 mmol) in chloroform (5 mL) was heated at reflux for 3 hours. The reaction mixture was diluted with ethanol, acidified with hydrochloric acid, and the precipitate was filtered off, suspended in ethanol and refluxed for 5 hours with bromoester **1a** (1.33 g 5.6 mmol) and triethylamine (0.8 mL, 5.6 mmol). After cooling, the precipitate was filtered off and appeared to be a mixture of **5i** and **5g** (64 : 36) according to ^{1}H NMR data. The mixture was separated by means of column chromatography using CH_2Cl_2–EtOH 10 : 1 as the eluent: d 0.4 gave 0.59 g (32%) of **5i**, mp 220 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.50 (6H, t, J = 7.2 Hz, $2CH_3$), 2.99 (6H, d, J = 5.2 Hz, $2NHCH_3$), 4.57 (4H, q, J = 7.2 Hz, $2OCH_2$), 5.10 (4H, s, $2CH_2$), 7.12 (2H, q, J = 5.2 Hz, 2NH). Anal. Calcd for $C_{20}H_{22}N_{12}O_6S_4$: C, 36.69; H, 3.39; N, 25.67. Found C, 36.64; H, 3.43; N, 25.60%.

5,5′-{4-Ethoxy-1,2-phenylenebis[(4-methyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-methyl-1,2,3-thiadiazole) 5j. Bromoester **1a** (1.0 g, 4.2 mmol) and 4-ethoxy-1,2-phenylenediamine **2j** (0.16 g, 1.0 mmol) were suspended in ethanol (30 mL) triethylamine (0.6 mL, 4.2 mmol) was added and the mixture was stirred at room temperature for 2 days. The precipitate was filtered off and crystallized from ethanol yielding 0.15 g (18%) of **5j**, mp 173 °C. ^{1}H NMR δ_H (DMSO-D_6 + CCl_4, 400 MHz): 1.22 (6H, t, J = 7.1 Hz, $2CH_3$), 1.43 (9H, t, J = 7.0 Hz, $3CH_3$), 4.18 (2H, q, J = 7.0 Hz, CH_2), 4.29 (2H, q, J = 7.1 Hz, OCH_2), 4.30 (2H, q, J = 7.1 Hz, OCH_2), 4.46 (2H, q, J = 7.1 Hz, OCH_2), 4.47 (2H, q, J = 7.1 Hz, OCH_2), 7.39 (1H, dd, J = 8.9, 2.8 Hz, C5H), 7.77 (1H, d, J = 2.8 Hz, C3H), 7.97 (1H, d, J = 8.9 Hz, C6H). ESI-MS 777 (MH^+). EIMS *m/z* (rel. int.): 530 (2), 502 (9), 430 (11), 330 (36), 302 (60), 258 (86), 229 (89), 202 (100). Anal. Calcd for $C_{28}H_{28}N_{10}O_9S_4$: C, 43.29; H, 3.63; N, 18.03. Found C, 43.34; H, 3.70; N, 18.10%.

5,5′-{4,5-Dimethyl-1,2-phenylenebis[(4-methyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-methyl-1,2,3-thiadiazole) 5k. Prepared from **1a** and **2k** as described for **5j**. Yield 35%, mp 210 °C. ^{1}H NMR δ_H (DMSO-D_6 + CCl_4, 250 MHz): 1.21 (6H,

t, J = 7.0 Hz, $2CH_3$), 1.43 (6H, t, J = 7.0 Hz, $2CH_3$), 2.43 (6H, s, $2CH_3$), 4.29 (4H, q, J = 7.0 Hz, $2CH_2$), 4.47 (4H, q, J = 7.3 Hz, $2CH_2$), 7.84 (2H, s, 2CH). ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 14.0, ($2CH_3$-triaz.), 14.3, ($2CH_3$-thiadiaz.), 20.1, (2 CH_3), 62.4, ($2OCH_2$-triaz.), 62.7, ($2OCH_2$-thiadiaz.), 128.2, (2CH-arom.), 129.1, (2NC-arom.), 134.4, (C5-triaz.), 141.3, (C4-triaz.), 142.3, ($2CH_3$*C*-arom.), 147.1, (C4-thiadiaz.), 158.9, (CO-triaz.), 160.2, (C5-thiadiaz.), 160.7 (CO-thiadiaz.). ESI-MS 761 (MH^+). EIMS *m*/*z* (rel. int.): 514(1), 486(6), 414(15), 314(15), 286(54), 242(59), 214(100), 157(23). Anal. Calcd for $C_{28}H_{28}N_{10}O_8S_4$: C, 44.20; H, 3.71; N, 18.41; S, 16.86. Found C, 44.16; H, 3.73; N, 18.35; S, 16.97%.

5,5′-{4-Methyl-1,2-phenylenebis[(4-methyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-methyl-1,2,3-thiadiazole) 5m. Prepared from **1a** and **2m** as described for **5j**. Yield 76%, mp 190 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.32 (6H, t, J = 7.2 Hz, $2CH_3$-triaz.), 1.470 (3H, t, J = 7.1 Hz, CH_3-thiadiaz.), 1.474 (3H, t, J = 7.1 Hz, CH_3-thiadiaz.), 2.55 (3H, dd, J = 0.9, 0.8 Hz, CH_3), 4.386 (2H, q, J = 7.2 Hz, OCH_2-triaz.), 4.388 (2H, q, J = 7.2 Hz, OCH_2-triaz.), 4.52 (2H, q, J = 7.2 Hz, OCH_2-thiadiaz.), 4.53 (2H, q, J = 7.2 Hz, OCH_2-thiadiaz.), 7.34 (1H, dq, J = 1.8, 0.9 Hz, C3H), 7.42 (1H, d, J = 8.2 Hz, C6H), 7.60 (1H, ddq, J = 8.2, 1.8, 0.8 Hz, C5H). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 13.95 (qt, J = 127.5, 2.6 Hz, $2CH_3$-triaz.), 14.20 (qt, J = 127.5, 2.6 Hz, $2CH_3$-thiadiaz.), 21.48 (qt, J = 128.4, 4.1 Hz, CH_3), 62.32 (tq, J = 148.9, 4.4 Hz, $2OCH_2$-triaz.), 62.66 (tq, J = 148.7, 4.3 Hz, OCH_2-thiadiaz.), 62.67 (tq, J = 148.9, 4.4 Hz, OCH_2-thiadiaz.), 128.19 (d, J = 167.6 Hz, C6-arom.), 128.24 (d, J = 8.0 Hz, C2-arom.), 129.10 (dddd, J = 164.3, 6.7, 5.5, 1.1 Hz, C3-arom.), 130.51 (dt, J = 8.7, 1.8 Hz, C1-arom.), 132.95 (dddq, J = 163.9, 9.0, 3.4, 1.8 Hz, C5-arom.), 134.26 (s, C5-triaz.), 134.39 (s, C5-triaz.), 141.30 (s, C4-triaz.), 141.43 (s, C4-triaz.), 143.75 (dq, J = 8.2, 5.9 Hz, C4-arom.), 147.05 (s, C4-thiadiaz.), 147.17 (s, C4-thiadiaz.), 158.81 (t, J = 3.2 Hz, CO-triaz.), 159.86 (s, C5-thiadiaz.), 160.01 (s, C5-thiadiaz.), 160.62 (t, J = 3.4 Hz, CO-thiadiaz.), 160.64 (t, J = 3.4 Hz, CO-thiadiaz.). ESI-MS 747 (MH^+). EIMS *m*/*z* (rel. int.): 472(15), 400(9), 300(13), 272(46), 228(67), 200(100), 116(36), 89(57). Anal. Calcd for $C_{27}H_{26}N_{10}O_8S_4$: C, 43.42; H, 3.51; N, 18.75; S, 17.17. Found C, 43.38; H, 3.59; N, 18.55; S, 17.00%.

Ethyl 5-[(1-methyl-2-{4-ethoxycarbonyl-5-[(4-ethoxycarbonyl-1,2,3-thiadiazol-5-yl)sulfanyl]-1*H*-1,2,3-triazol-1-yl}ethyl)-amino]-1,2,3-thiadiazole-4-carboxylate 6. A solution of bromoester **1a** (0.5 g, 2.1 mmol) and 0.75 equivalents of 1,2-propylenediamine **2b** (0.12 g) in chloroform (5 mL) was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in ethanol and kept for two days, The product slowly precipitated and was filtered off yielding 0.046 g (12%) of **6**, mp 178 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.33 (3H, t, J = 7.2 Hz, CH_3-triaz.), 1.44 (3H, t, J = 7.2 Hz, *CH_3*-thiadiaz.NH), 1.48 (3H, d, J = 6.5 Hz, CH_3), 1.52 (3H, t, J = 7.2 Hz, CH_3-thiadiaz.), 3.87 (1H, dqt, J = 8.9, 6.5, 6.2 Hz, CH), 4.38 (2H, q, J = 7.1 Hz, OCH_2-triaz.), 4.42 (2H, qd, J = 7.1, 1.8 Hz, O*CH_2*-thiadiaz.NH), 4.58 (2H, q, J = 7.2 Hz, OCH_2-thiadiaz.), 4.70 (1H, d, J = 6.2 Hz, CH2), 7.85 (1H, d, J = 8.9 Hz, NH). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 14.06 (qt, J = 127.5, 2.6 Hz, CH_3-triaz.), 14.33 (qt, J = 127.3, 2.6 Hz, *CH_3*-thiadiaz.NH + CH_3-thiadiaz.), 18.57 (qd, J = 128.8, 2.9 Hz, CH_3), 52.60 (t, J = 143.2 Hz, CH_2), 58.65 (d, J = 139.7 Hz, CH), 61.74 (tq, J = 148.2, 4.5 Hz, O*CH_2*-thiadiaz.NH), 62.32 (tq, J = 148.7, 4.3 Hz, OCH_2-triaz.), 62.93 (tq, J = 149.1, 4.5 Hz, OCH_2-thiadiaz.), 132.15 (t, J = 2.5 Hz, C5-triaz.), 132.43 (d, J = 1.5 Hz, C4-thiadiaz.NH), 141.72 (s, C4-triaz.), 147.14 (s, C4-thiadiaz.), 159.15 (t, J = 3.2 Hz, CO-triaz.), 159.87 (s, C5-thiadiaz.), 160.61 (t, J = 3.4 Hz, CO-thiadiaz.), 163.50 (t, J = 3.2 Hz, CO-thiadiaz.NH), 169.63 (dd, J = 3.8, 2.3 Hz, C5-thiadiaz.NH). ESI-MS 543 (MH^+). EIMS *m*/*z* (rel. int.): 514(3), 384(3), 352(68), 307(12), 235(100), 221(38), 139(55), 116(54), 85(86), 68(67). Anal. Calcd for $C_{18}H_{22}N_8O_6S_3$: C, 39.84; H, 4.09; N, 20.65. Found C, 39.92; H, 4.01; N, 20.49%.

Diethyl 9,10-dihydrobis[1,2,3]triazolo[1,5-*f*:5′,1′-*b*][1,3,6]-thiadiazepine-3,5-dicarboxylate 7a. A suspension of **5a** (1.0 g, 1.46 mmol) in ethanol (20 mL) with triethylamine (0.6 mL, 4.3 mmol) was refluxed and enough DMF was added to dissolve all the starting material. After 2 days of refluxing the reaction mixture was diluted with water (60 mL) and extracted with dichloromethane (3 × 20 mL). Evaporation of the solvent gave a crude product which was crystallized from ethanol to give 0.45 g (91%) of thiadiazepine **7a**, mp 192 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 1.45 (6H, t, J = 7.1 Hz, $2CH_3$), 4.47 (4H, q, J = 7.1 Hz, $2OCH_2$), 5.12 (4H, s, CH_2CH_2). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 14.21 (qt, J = 127.5, 2.6 Hz, $2CH_3$), 49.33 (tt, J = 146.6, 3.7 Hz, CH_2CH_2), 61.99 (tq, J = 148.7, 4.5 Hz, $2OCH_2$), 130.20 (tt, J = 1.5, 1.5 Hz, C5-triaz.), 138.04 (s, C4-triaz.), 159.89 (t, J = 3.4 Hz, CO). EIMS *m*/*z* (rel. int.): 338 (M^+, 100). Anal. Calcd for $C_{12}H_{14}N_6O_4S$: C, 42.60; H, 4.17; N, 24.84; S, 9.48. Found C, 42.53; H, 4.20; N, 24.91; S, 5.60%. When the ethanol filtrate combined with the water layer from extraction was acidified with HCl, the precipitated product (0.20 g) was characterized as bis(4-ethoxycarbonyl-1,2,3-thiadiazol-5-yl)disulfide **9**. The spectroscopic and analytical data of this product were identical to those reported earlier.[1]

Diethyl 9-methyl-9,10-dihydrobis[1,2,3]triazolo[1,5-*f*:5′,1′-*b*]-[1,3,6]thiadiazepine-3,5-dicarboxylate 7b. Prepared from **5b** as described for **7a**. Yield 73%, mp 168 °C. ^{1}H NMR δ_H (DMSO-D_6, 400 MHz): 1.33–1.37 (9H, m, $3CH_3$), 4.38 (2H, q, J = 7.1 Hz, CH_2), 4.39 (2H, q, J = 7.1 Hz, CH_2), 5.16, 5.27 (2H, AB-syst., J = 15.1, 5.5, 1.1 Hz, CH_2), 5.59 (1H, m, CH). ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 14.3 (CH_2CH_3), 14.3 (CH_2CH_3), 17.8 (CH_3), 53.0 (CH), 56.2 (CH_2), 62.0 (OCH_2), 62.1 (OCH_2), 129.4, 130.6, 137.4, 138.5, 159.8 (CO), 160.2 (CO). EIMS *m*/*z* (rel. int.): 352 (M^+, 100). Anal. Calcd for $C_{13}H_{16}N_6O_4S$: C, 44.31; H, 4.58; N, 23.85; S, 9.10. Found C, 44.38; H, 4.54; N, 23.97; S, 9.31%.

Diethyl 6,7-dihydro-5*H*-bis[1,2,3]triazolo[1,5-*g*:5′,1′-*b*]-[1,3,7]thiadiazocine-1,11-dicarboxylate 7c. Prepared from **5c** as described for **7a**. Yield 79%, mp 203 °C. ^{1}H NMR δ_H (DMSO-D_6 + CCl_4, 250 MHz): 1.41 (6H, t, J = 7.0 Hz, $2CH_3$), 2.19 (2H, m, $CH_2CH_2CH_2$), 4.28–4.48 (8H, m, $2OCH_2$ + $CH_2CH_2CH_2$). ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 14.3 ($2CH_3$), 27.7 ($CH_2CH_2CH_2$), 44.9 ($2NCH_2$), 62.1 ($2OCH_2$), 131.3, 138.5, 160.2 (2CO). EIMS *m*/*z* (rel. int.): 352 (M^+, 100). Anal. Calcd for $C_{13}H_{16}N_6O_4S$: C, 44.31; H, 4.58; N, 23.85. Found C, 44.29; H, 4.61; N, 23.80%.

2-Ethoxy-8,10-bis(ethoxycarbonyl)di[1,2,3]triazolo[1,5-*a*;5′,1′-*d*][3,1,5]benzothiadiazepine 7j. To a solution of **1a** (1.0 g, 4.22 mmol) and 4-ethoxy-1,2-phenylenediamine **2j** (0.33 g 2.1 mmol) in ethanol (80 mL), triethylamine (0.6 mL, 4.2 mmol) was added and the reaction mixture was refluxed overnight. Then a second portion of triethylamine (1.2 mL) was added and soon the product precipitated from the boiling solution. After refluxing for an additional hour, the reaction mixture was cooled, and the product was filtered off and crystallized from ethanol yielding 0.38 g (42%) of thiadiazepine **7j**, mp 168 °C. ^{1}H NMR δ_H (DMSO-D_6 + CCl_4, 250 MHz): 1.42 (3H, t, J = 7.0 Hz, CH_2), 1.43 (3H, t, J = 7.0 Hz, CH_3), 1.47 (3H, t, J = 7.0 Hz, CH_3ethoxy), 4.26 (2H, q, J = 7.0 Hz, OCH_2ethoxy), 4.40 (2H, q, J = 7.0 Hz, OCH_2), 4.41 (2H, q, J = 7.0 Hz, OCH_2), 7.41 (1H, dd, J = 9.2, 2.7 Hz, C3H), 7.52 (1H, d, J = 2.7 Hz, C1H), 7.99 (1H, d, J = 9.2 Hz, C4H). EIMS *m*/*z* (rel. int.): 430 (M^+, 18). Anal. Calcd for $C_{18}H_{18}N_6O_5S$: C, 50.23; H, 4.22; N, 19.52; S, 7.45. Found C, 50.31; H, 4.20; N, 19.70; S, 7.20%.

Ethyl 5-[1-(2-amino-4-ethoxyphenyl)-4-ethoxycarbonyl-1,2,3-triazol-5-ylsulfanyl]-1,2,3-thiadiazole-4-carboxylate 8j. A solution of **12j** (0.9 g, 2.9 mmol) and triethylamine (0.8 mL, 5.7 mmol) in ethanol (50 mL) was refluxed for 3 hours, then cooled to room temperature and bromoester **1a** (0.7 g, 2.9 mmol) was added. The reaction mixture was stirred for 1 h and a half of the solvent was removed. The product that precipitated from the solution upon cooling was filtered off and crystallized from ethanol (1.16 g) 86%, mp 130 °C. ^{1}H NMR δ_H (DMSO-D_6 + CCl_4, 250 MHz): 1.23 (3H, t, J = 7.0 Hz, CH_3ethoxy), 1.35 (3H, t, J = 7.0 Hz, CH_3), 1.41 (3H, t, J = 7.0 Hz, CH_3), 3.97 (2H, q, J = 7.0 Hz, OCH_2ethoxy), 4.30 (2H, q, J = 7.0 Hz, OCH_2), 4.43 (2H, q, J = 7.0 Hz, OCH_2), 5.22 (2H, br s, NH_2), 6.14 (1H, dd, J = 8.5, 2.5 Hz, C5H), 6.35 (1H, d, J = 2.5 Hz, C3H), 6.94 (1H, d, J = 8.5 Hz, C6H). EIMS *m*/*z* (rel. int.): 464 (M^+, 6), 205 (100). Anal. Calcd for $C_{18}H_{20}N_6O_5S_2$: C, 46.54; H, 4.34; N, 18.09; S, 13.81. Found C, 46.60; H, 4.37; N, 17.98; S, 13.40%.

Ethyl 5-[*N*-(2-amino-4-ethoxyphenyl)amino]-1,2,3-thiadiazole-4-carboxylate 12j. A solution of ethyl 5-bromo-1,2,3-thiadiazole-4-carboxylate **1a** (1.71 g, 7.2 mmol) and diamine **2j** (2.2 g, 14.5 mmol) in DMF (20 mL) was stirred at room temperature, and the reaction was monitored with TLC. After the starting compound had disappeared, the reaction mixture was diluted with water. The precipitate was filtered off and crystallized from ethanol (0.94 g) 56%, mp 145 °C. ^{1}H NMR δ_H (DMSO-D_6 + CCl_4, 250 MHz): 1.35 (3H, t, J = 7.0 Hz, CH_3), 1.42 (3H, t, J = 7.0 Hz, CH_3), 3.96 (2H, q, J = 7.0 Hz, OCH_2), 4.41 (2H, q, J = 7.0 Hz, OCH_2), 5.01 (2H, br s, NH_2), 6.12 (1H, dd, J = 8.5, 2.4 Hz, C5H), 6.33 (1H, d, J = 2.4 Hz, C3H), 6.96 (1H, d, J = 8.5 Hz, C6H), 8.98 (1H, s, NH). EIMS *m*/*z* (rel. int.): 308 (M^+, 81). Anal. Calcd for $C_{13}H_{16}N_4O_3S$: C, 50.64; H, 5.23; N, 18.17; S, 10.40. Found C, 50.61; H, 5.28; N, 18.10; S, 10.37%.

9,10-Dihydrobis[1,2,3]triazolo[1,5-*f*:5′,1′-*b*][1,3,6]thiadiazepine-3,5-dicarboxylic acid 10. To an aqueous solution of NaOH (0.36 g, 9.0 mmol in 100 mL), thiadiazepine **7a** (1.52 g, 4.5 mmol) was added and the suspension was refluxed until a clear solution formed, then this was acidified with conc. HCl and the precipitated acid filtered off as colourless crystals (1.05 g, 83%), mp 213 °C. ^{1}H NMR δ_H (DMSO-D_6, 400 MHz): 5.08 (4H, s, $2CH_2$). EIMS *m*/*z* (rel. int.): 282 (M^+, 2), 238(46), 194(51). Anal. Calcd for $C_8H_6N_6O_4S$: C, 34.05; H, 2.14; N, 29.78; S, 11.36. Found C, 34.11; H, 2.17; N, 29.49; S, 11.53%.

9,10-Dihydrobis[1,2,3]triazolo[1,5-*f*:5′,1′-*b*][1,3,6]thiadiazepine 11. Acid **10** (1.70 g, 6.0 mmol) was heated at 175 °C in DMSO (20 mL) for 8 hours. The DMSO was removed *in vacuo* and the residue was washed with ethanol to give **11** (1.13 g, 97%), mp 156 °C. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz): 5.09 (4H, s, CH_2CH_2), 7.76 (2H, s, 2CH-triaz.). ^{13}C NMR δ_C ($CDCl_3$, 100 MHz): 47.78 (tt, J 145.8, 3.7 Hz, CH_2CH_2), 124.60 (dt, J 14.7, 1.3 Hz, C5-triaz.), 134.72 (d, J 199.3 Hz, C4-triaz.). EIMS *m*/*z* (rel. int.): 194 (M^+, 100). Anal. Calcd for $C_6H_6N_6S$: C, 37.11; H, 3.11; N, 43.27; S, 16.51. Found C, 37.06; H, 3.13; N, 43.35; S, 16.75%.

Single crystals of compound **11** suitable for X-ray diffraction were obtained by crystallization from ethanol.

Crystal structure determination of compound **11**:†

Crystal data: $C_6H_6N_6S$, M = 194.24, monoclinic, a = 13.4019(2), b = 8.1355(1), c = 7.8447(1) Å, β = 101.744(1), U = 837.41(2) Å^3, T = 299(1) K, space group $P2_1/c$ (no. 14), Z = 4, μ(Cu–K_α) = 3.129 mm^{-1}, 5685 measured reflections, 1513 unique (R_{int} = 0.046) which were used in all calculations. The final $R1$ = 0.0437 (for 1421 data with $I > 2\sigma(I)$) and $wR2$ = 0.1405 (all data).

Acknowledgements

We thank the Russian Foundation for Basic Research (grant 01-03-32609 and 00-03-40139) and CRDF RC-2393-EK-02 for financial support. We also thank the F. W. O. - Vlaanderen, the Ministerie voor Wetenschapsbeleid, INTAS and the University of Leuven for financial support.

† CCDC reference number 214711. See http://www.rsc.org/suppdata/ob/b3/b307693h/ for crystallographic data in .cif or other electronic format.

References

1 N. N. Volkova, E. V. Tarasov, L. Van Meervelt, S. Toppet, W. Dehaen and V. A. Bakulev, *J. Chem. Soc., Perkin Trans. 1*, 2002, **13**, 1574.
2 N. N. Volkova, E. V. Tarasov, W. Dehaen and V. A. Bakulev, *Chem. Commun.*, 1999, 2273–2274.
3 (*a*) Yu. Yu. Morzherin, E. V. Tarasov and V. A. Bakulev, *Khim. Geterotsikl. Soedin.*, 1994, **4**, 554–559; (*b*) G. L'abbé and E. Vanderstede, *J. Heterocycl. Chem.*, 1989, **26**, 1811–1814.
4 D. Kotkar, S. W. Mahajan, A. K. Mandal and P. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1749–1752.
5 (*a*) R. Okazaki, T. Hasegawa and Y. Shishido, *J. Am. Chem. Soc.*, 1984, **106**, 5271–5273; (*b*) S. Ito, A. Ota, H. Suhara, K. Tabashi and Y. Kawashima, *Chem. Pharm. Bull.*, 1993, **41**, 1066–1073.
6 R. B. Katz, M. B. Mitchell and P. G. Sammes, *Tetrahedron*, 1989, **45**, 1801–1814.
7 F. Trecourt and G. Queguiner, *J. Chem. Res.*, 1982, (S) 76–77; (M) 912–942.
8 M. Witanowski and Z. Biedrzycka, *Magn. Reson. Chem.*, 1994, **32**, 62–66.