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Synthesis and Study of the Rearrangements of 5-(1,2,3-Triazol-4-yl)-1,2,3-thiadiazoles*

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Abstract: A method for the synthesis of heterocyclic ring conjugates containing 1,2,3-thiadiazole and 1,2,3-triazole nuclei was elaborated. The mechanism of rearrangement (effect of substituents and solvents) was investigated by NMR spectroscopy. A novel domino-type rearrangement involving both heterocycles was discovered. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Polynitrogen and sulfur-containing heterocycles may undergo various ring transformations that are often accompanied by ring opening and rearrangements.[1] The biological activity and the chemical properties of 1,2,3-triazoles and 1,2,3-thiadiazoles are linked to their ring transformations.[2,3] However, there are so far no data in the literature about rearrangements where more than one of these heterocyclic rings are involved at the same time, probably due to the lack of a suitable way of synthesizing the necessary arrays of 1,2,3-triazole and 1,2,3-thiadiazole rings.

RESULTS AND DISCUSSION

(i) Synthesis and rearrangements of 5-(1,2,3-triazol-4-yl)-1,2,3-thiadiazoles

Retrosynthetically, Scheme **1** can be proposed starting from 1,2,3-thiadiazoles **4**.[4] One of the approaches involves the generation of diazoacetamides by means of the diazo transfer reaction, which subsequently cyclize to 5-hydroxy-1,2,3-triazoles.[5] Examples of these reactions where the methylene group is activated by a heterocyclic ring are relatively scarce.[6] Diazo group transfer reactions to hetarylacetamides were not described so far.

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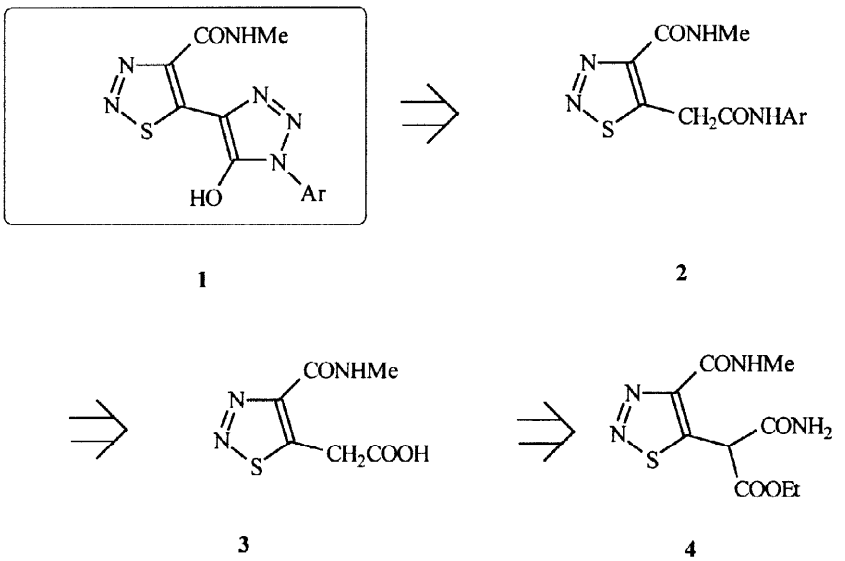
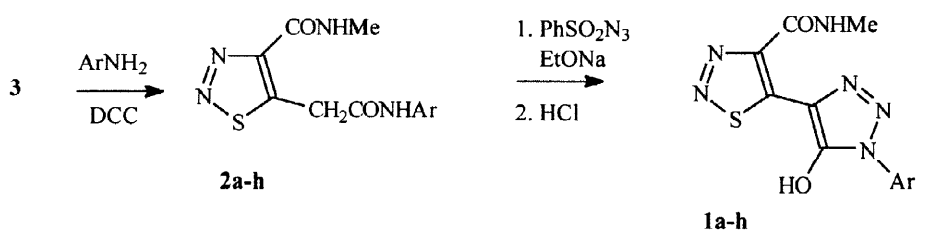


Scheme 1

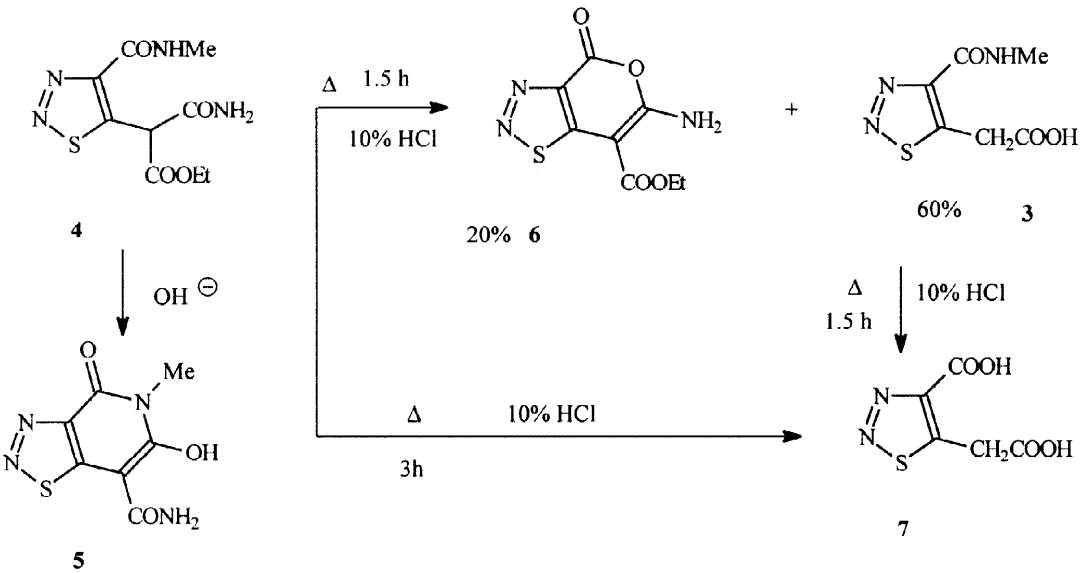
Compounds of type **2** were prepared from acid **3** (Scheme 2), which in turn could be synthesized from the amido-ester **4** by hydrolysis in acid medium (Scheme 3). It should be noted that the presence of two amide groups together with an ester functionality complicates the reaction course.



1,2 a Ar = Ph
b Ar = 4-MeC_6H_4
c Ar = 2-$MeOC_6H_4$
d Ar = 4-$MeOC_6H_4$
e Ar = 3-ClC_6H_4
f Ar = 4-ClC_6H_4
g Ar = 2,6-$Cl_2C_6H_3$
h Ar = 4-BrC_6H_4

Scheme 2

In fact, the treatment of compound **4** with an aqueous sodium hydroxide solution gives the cyclization product, thiadiazolo[4,5-*c*]pyrid-4-one **5**, instead of the acid **3**[4] (Scheme 3). The desired acid **3** could be formed in a mixture together with pyrano[4,5-*c*]1,2,3-thiadiazole **6** after refluxing of compound **4** in 10% HCl . The structure of **6** was proved by comparison with a authentic sample of this compound prepared by another method.[4] The ^1H NMR spectrum of **3** shows a singlet for the methylene group at δ 4.5 ppm, a quartet for the NHMe at δ 8.9 ppm and a doublet for the methyl group (NHMe) at 2.8 ppm. The optimal reaction time was found to be 1.5 h where compounds **6** and **3** were formed in 20 and 60% yields respectively. On further heating of **4** the products **6** and **3** were accompanied by the diacid **7**.

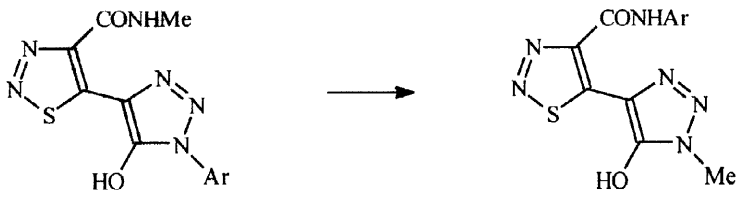


Scheme 3

Acid **3** was converted to anilides **2a-h** in high yields by its reaction with anilines in acetone in the presence of dicyclohexylcarbodiimide (Scheme **2**). The ^{1}H NMR spectra of compounds **2a-h** contain the expected signals for the aryl ring, as well as singlets for the methylene groups at δ 4.7 ppm.[7] The reactions of the amides **2a-h** with benzenesulfonyl azide in the presence of sodium ethoxide in alcohol with subsequent treatment of dilute hydrochloric acid afforded the desired 1,2,3-triazoles **1a-h** in high yields. The ^{1}H NMR spectra of the bisheterocycles **1a-h** show, besides the signals of aromatic protons at 6.0 - 7.0 ppm, a quartet for the NH protons at 10 ppm and a doublet for the NH-Me group at 2.8 ppm. The ^{13}C NMR spectra of compounds **1a-h** contain the signals for the 1,2,3-triazole ring at 144.2 - 145.9 (C_4), 144.4 -150 (C_5) ppm, for the thiadiazole ring at 115.5 - 128.8 (C_4) and 144.2 - 151.4 (C_5) ppm, for the carbonyl group at 162.1 -162.3 ppm and for the methyl group at 26.8 - 26.9 ppm, together with the expected signals for the aryl ring at 129 - 140 ppm.

Thus we elaborated a convenient method for the preparation of novel conjugated heterocycles of type **1** in 30% overall yield. However, we could not prepare compounds **1** with an alkyl group at the nitrogen atom of the triazole ring because of the very poor yield in preparing alkylamides of type **2** (R^1 = alkyl).

We have discovered that the bisheterocycles **1a-h** are prone to rearrange to isomeric products **8a-h** on heating in various organic solvents (scheme **4**). This process was found to evolve very slowly. Boiling of **1c,e-h** in ethanol for 24 hr afforded the rearrangement products **8c,e-h** in 40 - 50 % yields. The separation of compounds **8c,e-h** from **1c,e-h** was possible because of the lower solubility of the latter in comparison with the corresponding starting materials **1c,e-h**.



1a-h **8a-h**

a Ar = Ph
b Ar = 4-MeC_6H_4
c Ar = 2-$MeOC_6H_4$
d Ar = 4-$MeOC_6H_4$
e Ar = 3-ClC_6H_4
f Ar = 4-ClC_6H_4
g Ar = 2,6-Cl_2C_6H
h Ar = 4-BrC_6H_4

Scheme 4

This process did not take place for the compounds **1a,b,d** bearing electron-donating substituents at the aromatic ring making the triazole more stable. The rearranged products were not detected, even after refluxing of **1a,b,d** in ethanol for 40 h. The use of pyridine as the solvent instead of ethanol allowed us to obtain **8b** as a mixture with the starting material **1b** (ratio 1:3). Finally, we succeeded to prepare **8a,b,d** by heating of **1a,b,d** in DMF at 100° C for 25 h.

Compounds **8a-h** could easily be distinguished from **1a-h** because of the absence of quartet and doublet signals of the NHMe group in their ^{1}H NMR spectra. The NHAr protons of products **8** resonate at 11 ppm and the Me groups at 3.8 ppm, which is typical for a methyl group at the nitrogen of a heteroaromatic ring.[8] The ^{13}C NMR spectra of compounds **8** are similar to those for bicycles **1**.

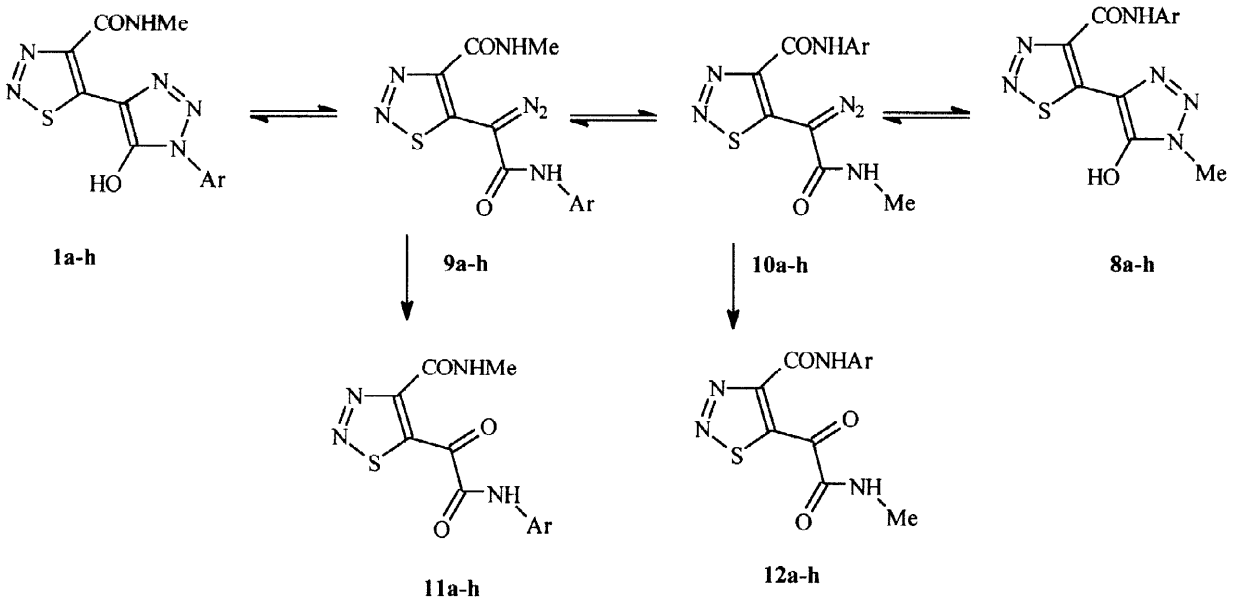
Thus, this new rearrangement is a synthetic alternative towards compounds of type **1** and now allows one to prepare derivatives containing an alkyl group at the position 1 of the triazole ring.

ii) Study of the Mechanism of Rearrangement

This new rearrangement is believed to proceed as a multistep process and involves ring opening of the triazole ring of **1** to form the diazo compound **9**, which rearranges to the isomeric diazo compound **10**, followed by cyclization to the final product **8** (scheme **5**).

In an effort to identify the intermediates we have followed the progress of the reaction of compounds **1** by ^{1}H, ^{13}C NMR and IR spectroscopy. The IR spectrum of the reaction mixture of compound **1c** shows a signal at 2095 cm^{-1} which is typical for a diazo group. The ^{1}H NMR spectra during the reaction course show, besides the signals of the starting materials **1a-h** and final products **8a-h**, additional signals at 2.86 - 2.89 and 2.79 - 2.81 ppm (see tables 1,2,3), attributed to the protons of the NHMe groups of the diazo compounds **9a-h** and **10a-h**. Although in general the concentration of the diazo compounds in the reaction mixtures was too low, in one case, for diazocompounds **9g** and **10 g** , the ^{13}C NMR signals could be detected. These spectra contain besides the signals of the carbonyl function, the aromatic and heteroaromatic rings at respectively 162.63 (CONHAr),

160.63 (CONHMe), 133.95 (C_o), 129.86 (C_p), 128.65 (C_m), 132.10 (C_i), 144.39 (C_4), 145.87 (C_5), 25.92 ppm (CH_3), a signal at 62.79 ppm, which was assigned to the diazo group.[9]



Scheme 5

When compounds **1c,g** were dissolved in DMSO-d_6 a mixture of **1c,g** and diazo compounds **9c,g**. was obtained. Heating of **1c,g** in DMSO-d_6 gave initially the diazo compounds **9c,g**. Later, additional signals for the diazo compounds **10c,g** appeared in the ^{1}H NMR spectra. In agreement with this, heating of the rearrangement product **8c** lead to the sequential formation of diazo compounds **10c** and **9c**.

It is well known that diazo compounds are rather labile compounds which easily loose nitrogen when heated. The heating of the triazolo-thiadiazoles **1a-h** in DMSO in the presence of water at 130° C lead to the evolution of nitrogen and the formation of the ketones **11a-h** and **12a-h**. The ^{1}H NMR spectra of **11a-h** and **12a-h** contain the doublet signals of the NHMe group at 2.83 and 2.78 ppm, respectively, and the signals of the aromatic protons at 7.3-7.9 ppm. In the ^{13}C NMR spectra, the signals of the carbonyl groups were detected at 179-180 ppm, together with the signals of the carbamoyl and heteroaromatic groups. It should be noted that heating of **8c** under the same conditions lead to the same mixture of ketones **11c** and **12c**.

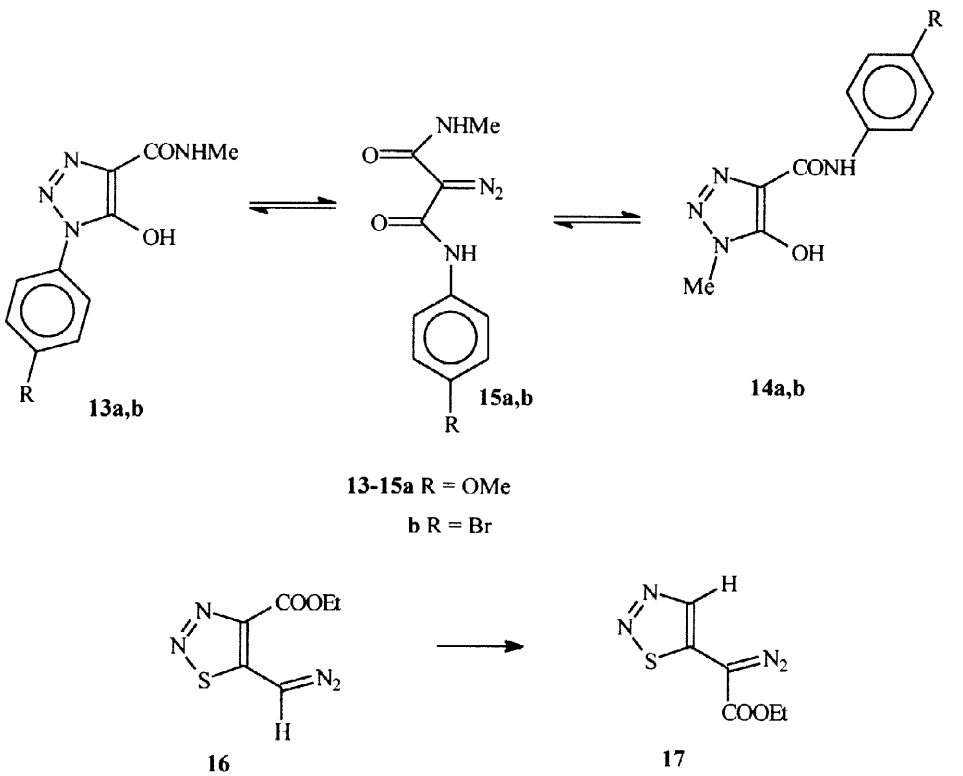
Based on the data mentioned above, we can conclude that the rearrangement occurs via the intermediate diazo compounds **9** and **10** and involves three steps: (i) the ring opening of the triazole to form the diazo compound **9**, (ii) rearrangement of **9** to the isomeric **10** with participation of three ring atoms[10] and (iii) cyclization of **10** to the final products **8**.

The driving force for the rearrangement of **16** to **17**, as shown by L'abbé and co-workers,[11] is the stabilization of the diazo compound **17** by the carbonyl group. The structures of the diazo compounds **9** and **10** are not that different as those of the diazo compounds **16** and **17** (Scheme 6). Therefore a substituent effect on the equilibrium between diazo compounds **9** and **10** will be small.

Table 1. The ^{1}H chemical shift and multiplicity of compounds **1,8,9,10,11,12** in DMSO-d6.

Compound	**^{1}H NMR spectra (δ, DMSO-d_6)**				
	NMe	N*H*Me	N*H*Ar	ArH	ArR
1a	2.98 d	10.16 br q		7.85 d, 7.60 dd, 7.50 dd	
8a	3.77 s		11.42 s	7.82 d, 7.40 dd, 7.22 dd	
9a	2.88 d	8.42 br q	10.20 s	7.80 d, 7.56 dd, 7.47 dd	
10a	2.80 d	8.16 br q	10.80 s	7.79 d, 7.35 dd, 7.12 dd	
11a	2.84 d	8.67 br q	10.95 s	7.80 d, 7.37 dd, 7.17 dd	
12a	2.78 d	8.20 br q	10.70 s	7.70 d, 7.37 dd, 7.17 dd	
1b	2.99 d	10.05 br q		7.39 d, 7.01 d	2.39 s
8b	3.77 s		11.30 s	7.56 d, 7.18 d	2.30 s
9b	2.89 d	8.27 br q	10.21 s	7.44 d, 7.21 d	2.25 s
10b	2.79 d	8.05 br q	10.77 s	7.69 d, 7.17 d	2.27 s
11b	2.84 d	8.78 br q	10.70 s	7.69 d, 7.20 d	2.28 s
12b	2.78 d	9.05 br q	10.50 s	7.71 d, 7.21 d	2.31 s
1c	2.97 d	10.11 br q		7.48 dd, 7.15 ddd, 7.61 ddd, 7.31 dd	3.81 s
8c	3.69 s		10.92 s	8.12 dd, 7.23 ddd, 7.04 ddd, 7.16 dd	3.91 s
9c	2.89 d	9.01 br q	9.97 s	8.21 dd, 7.01 ddd, 7.22 ddd, 7.16 dd	3.81 s
10c	2.80 d	8.53 br q	10.89 s	8.09 dd, 7.58 ddd, 7.28 ddd, 7.44 dd	3.85 s
11c	2.86 d	9.08 br q	11.09 s	8.11 dd, 7.18 ddd, 7.03 ddd, 7.16 dd	3.84 s
12c	2.76 d	9.86 br q	10.95 s	8.22 dd, 7.19 ddd, 7.01 ddd, 7.11 dd	3.93 s
1d	2.98 d	10.80 br q		7.25 d, 7.55 d	3.88 s
8d	3.76 s		10.50 s	6.94 d, 7.72 d	3.75 s
9d	2.86 d	8.4 br q	10.60 s	6.92 d, 7.75 d	3.76 s
10d	2.80 d	9.07 br q	10.51 s	6.89 d, 7.73 d	3.76 s
11d	2.83 d	8.70 br q	11.40 s	6.95 d, 7.78 d	3.76 s
12d	2.77 d	9.05 br q	10.70 s	6.96 d, 7.61 d	3.77 s
1e	2.99 br s	10.17 br s		8.02 dd, 7.89 ddd, 7.62 ddd, 7.53 ddd	
8e	3.77 s		10.92 s	7.87 dd, 7.76 ddd, 7.43 ddd, 7.21 ddd	
9e	2.88 d	8.83 br q	9.97 s	7.98 dd, 7.73 ddd, 7.42 ddd, 7.17 ddd	
10e	2.81 d	8.42 br q	10.89 s	7.71 dd, 7.78 ddd, 7.42 ddd, 7.22 ddd	
11e	2.78 d	9.08 br q	11.09 s	8.00 dd, 7.58 ddd, 7.42 ddd, 7.22 ddd	
12e	2.76 d	9.86 br q	10.95 s	7.88 dd, 7.58 ddd, 7.43 ddd, 7.24 ddd	
1f	2.98 br s	9.60 br s		7.96 d, 7.62 d	
8f	3.75 s		10.60 s	7.86 d, 7.38 d	
9f	2.86 d	9.11 br q	10.70 s	7.77 d, 7.38 d	
10f	2.80 d	8.50 br q	10.90 s	7.84 d, 7.38 d	
11f	2.83 d	9.07 br q	11.70 s	7.70 d, 7.39 d	
12f	2.78 d	8.80 br q	10.30 s	7.86 d, 7.39 d	
1g	2.98 d	10.25 br q		7.82 dd, 7.72 dd	
8g	3.72 s		10.95 s	7.45 dd, 7.64 dd	
9g	2.87 d	9.01 br q	10.63 s	7.61 dd, 7.44 dd	
10g	2.79 d	8.53 br q	10.89 s	7.43 dd, 7.59 dd	
11g	2.83 d	9.08 br q	11.09 s	7.59 dd, 7.41 dd	
12g	2.74 d	9.86 br q	10.95 s	7.42 dd, 7.60 dd	
1h	2.98 br s	10.10 br q		7.89 d, 7.75 d	
8h	3.75 s		11.64 s	7.83 d, 7.58 d	
9h	2.86 d	8.82 br q	8.70 s	7.80 d, 7.53 d	
10h	2.80 d	8.42 br q	10.41 s	7.84 d, 7.53 d	
11h	2.83 d	9.99 br q	11.07 s	7.81 d, 7.58 d	
12h	2.78 d	9.19 br q	10.90 s	7.67 d, 7.58 d	

The new rearrangement is analoguous to the rearrangement of 1-Ar-4-(N-methyl)carbamoyl-1,2,3-triazoles **13** to 1-methyl-4-N-Ar-carbamoyl-1,2,3-triazoles **14**, proceeding via diazo compounds **15** , which also involves ring opening and ring closure to 5-hydroxy-1,2,3-triazoles[12] (scheme 6). Bakulev and co-workers have shown that the rearrangement of 1-Ar-4-(N-methyl)carbamoyl-1,2,3-triazoles **13** to 1-methyl-4-N-Ar-carbamoyl-1,2,3-triazoles **14**, is reversible and the equilibrium is shifted to 1-methyltriazoles **14** in polar solvents and to the open structure **15** in nonpolar solvents.[12] As the difference in structure between the two diazo compounds **9** and **10** is not very large, the position of the equilibrium between **1** and **8** will be governed by the same factors that influenced the equilibrium between **13 a,b** and **14 a,b**.



Scheme 6

To study the mechanism of the rearrangement (effect of substituents and solvent) we have carried out a kinetic study of **1a-h** by ^{1}H NMR spectroscopy in DMSO-d_6, pyridine-d_5 and methanol-d_4 at 60° C. The relative concentrations of **1**, **9**, **10** and **8** were determined by their relative signal intensity whereby the added dicyclohexyl urea and TMS were used as reference. All measurements were made at 60° C, since then the rearrangement of the starting compounds **1** to the final products **8c,e,f** is irreversible. The reactions all reached completion (less than 0.5 % of **1a-h**) so we can conclude that the equilibrium is shifted in favour of the N-alkyltriazoles **8a-h**. The intermediate diazo compounds **9** and **10** were formed already at the initial stage of the

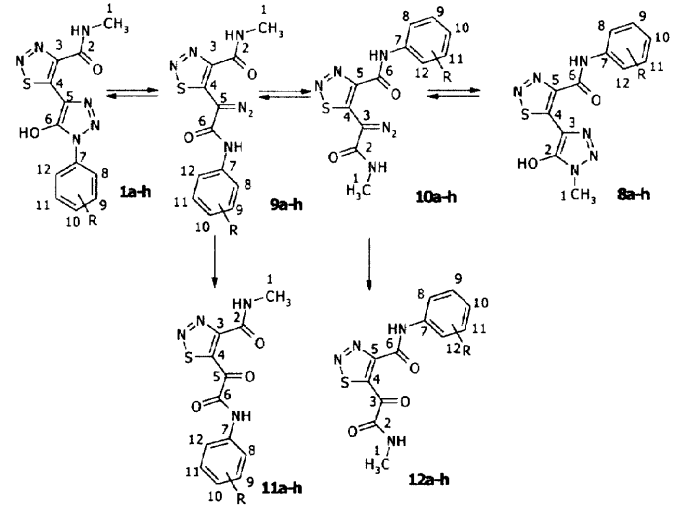


Table 3. The ^{13}C chemical shift and multiplicity of compounds **1,8,9,10,11,12** in DMSO-d_6.

	The ^{13}C Chemical shift, DMSO-d_6												
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	R
1b	26.8 qd	162.1 m	142.6 m	148.2 s	115.7 m	150.4 m	145.6 s	121.8 dd	129.8 ddq	138.1 q			20.7 qt
1c	26.9	162.3	144.2	150.0	128.8	150.1	145.1	120.6	128.5	112.9	132.1	154.3	56.00
8c	31.8	*	*	*	*	159.5	146.6	120.5	122.3	111.5	126.0	150.3	55.99
11c	26.0	159.9	149.2	147.4	179.0	158.4	145.0	121.9	125.5	111.4	126.3	149.8	55.8
12c	25.9	157.8	180.6	146.8	148.8	159.0	145.3	120.3	125.8	111.5	128.3	149.8	56.0
1g	26.9 q	162.1 q	145.9 br s	144.4 br s	115.3 s	151.4 m	129.5 s	133.6 dt	129.2 dd	133.3 d			
8g	31.8	156.8	116.8	145.0	156.8	160.8	130.6	132.24	129.6	133.8			
9g	25.9 q	160.6 q	145.9 s	144.4	62.8 s	162.6 d	132.1 d	133.9 dq	128.6 dd	129.9 d			
10g	25.8	162.0	60.8	145.4.	155.9	161.0	129.6	134.0	130.2	133.4			
11g	25.8	159.8	147.9	143.3	178.8	160.47	130.4	134.0	129.0	133.8			
12g	25.9	158.1	179.5	145.4	147.4	159.9	133.4	132.0	129.9	133.9			

* The solubility in DMSO-d_6 was too low to observe these values.

reaction, but their concentration never reached more than 10 % in the reaction mixture. Notable exceptions are the ortho-substituted derivatives **1c,g** which upon dissolving in DMSO-d_6 and deuterated methanol are

Table 2. The ^{1}H chemical shift and multiplicity of compounds **1,8,9,10,11,12** in methanol-d_4.

Compound	^{1}H NMR spectra (δ, methanol-d_4)		
	NMe	ArH	ArR
1a	3.11 s	7.888 d, 7.57 dd, 7.48 dd	
8a	3.84 s	7.81 d, 7.55 dd, 7.41 dd	
9a	3.00 s	7.82 d, 7.46 dd, 7.35 dd	
10a	2.92 s	7.71 d, 7.55 dd, 7.21 dd	
1b	3.10 s	7.74 d, 7.36 dd	2.42 s
8b	3.80 s	7.69d, 7.22 d	2.37 s
9b	3.00 s	7.74 d, 7.35 d	2.33 s
10b	2.90 s	7.73 d, 7.36 d	2.34 s
1c	3.09 s	7.13 dd, 7.40 ddd, 7.24 ddd, 7.56 dd	3.92 s
8c	3.78 s	7.18 dd, 7.00 ddd, 7.08 ddd, 8.32 dd	3.96 s
9c	3.02 s	7.18 dd, 6.99 ddd, 7.03 ddd, 8.37 dd	3.93 s
10c	2.82 s	7.16 dd, 6.96 ddd, 7.01 ddd, 8.30 dd	3.82 s
1d	3.10 s	7.76 d, 7.06 d	3.87s
8d	3.87 s	7.76 d, 7.06 d	3.87 s
9d		<0.5%	
10d		<0.5%	
1e	3.11 s	8.00 dd, 7.48 ddd, 7.55 ddd, 7.89 ddd	
8e	3.84 s	8.00 dd, 7.72 ddd, 7.20 ddd, 7.40 ddd	
9e	3.00 s	7.91 dd, 7.71 ddd, 7.45 ddd, 7.59 ddd	
10e	2.92 s	7.90 dd, 7.71 ddd, 7.52 ddd, 7.33 ddd	
1f	3.10 s	7.92 d, 7.56 d	
8f	3.83 s	7.08 d, 6.72 d	
9f	3.00 s	7.84 d, 7.32 d	
10f	2.92 s	7.57 d, 7.38 d	
1g	3.10 s	7.64 d, 7.49 dd	
8g	3.81 s	7.52 d, 7.36 dd	
9g	3.01 s	7.65 d, 7.33 dd	
10g	2.91 s	7.49 d, 7.33 dd	
1h	3.10 s	7.89 d, 7.68 d	
8h	3.75 s	7.82 d, 7.52 d	
9h	3.00 s	7.89 d, 7.68 d	
10h	2.93 s	7.82 d, 7.52 d7	

Table 4. The half-lifes of **1a-h** in different solvents.

Compound	The half-lifes (h)		
	DMSO-d_6	methanol-d_4	Pyridine-d_5
	τ	τ	τ
1a	18.5	494.8	
1b	28.4	972.2	223.8
1c	16.4	115.3	37.5
1d	82.6	1336.8	250.0
1e	9.3	118.8	
1f	16.2	325.7	229.0
1g	10.0	81.2	59.4
1h	16.9	350.0	

converted to approximately 40 % of the corresponding diazo compounds **9** and **10**. In this way, we have measured the half-lifes of **1a-h** in order to evaluate the solvent and substituent effect on the kinetics of the reaction (Table 4). Based on the data in Table 4, the following conclusions can be made : i) the half-lifes

decrease in the following order : DMSO > pyridine > methanol, which can be attributed to a combination of the effects of polarity and hydrogen bond capacity, ii) a positive correlation is observed for the *para*-and *meta*-substituted derivatives **1a,b,d,e,f,h** between their half-lifes and the Hammett constants. These findings are in good accordance with the literature data on the equilibrium of α-diazoimines and 1,2,3-triazoles[6].

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EXPERIMENTAL SECTION

The ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-80 and Bruker AMX 400 with TMS as internal reference. IR spectra were obtained on a Specord UR-20 spectrometer as KBr pellets. Products were analyzed by TLC on DC-Plastikfolen Kieselgel 60 F 254. The melting points were uncorrected.

2-(4-(N-Methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetic acid (3):

Compound **4** (1g, 3.67 mmol) was suspended in 10% HCl (30 mL) and boiled during 1.5 h. The product **6** was separated by hot filtration and the filtrate was cooled to 0° C. The precipitate **3** was collected by filtration, washed with ice-cold water (2x10 mL) and dried *in vacuo*. Yield 60-65%; mp 210-212°C (from water); ^1H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 12.39 (1H, br s, OH), 8.97 (1H, q, *J*=5.2 Hz, N*H*Me), 4.53 (2H, s, CH_2), 2.84 (3H, d, *J*=5.2 Hz, NHCH_3); Anal. calcd. for $C_6H_7N_3O_3S$, %: C 35.82, H 3.51, N 20.88, S 15.94; Found, %: C 36.07, H 3.53, N 20.74, S 16.03.

2-(4-Carboxy-1,2,3-thiadiazol-5-yl)acetic acid (7):

Compound **7** was obtained by analogy with **3** (duration 3h) Yield 56%; mp 192°C (from water); ^1H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 13.29 (2H, br s, OH), 4.48 (2H, s, CH_2); IR (ν_{max}, cm^{-1}): 1710 (C=O), 1690 (C=O), 1510, 1320; Anal. calcd. for $C_5H_4N_2O_4S$, %: C 31.92, H 2.14, N 14.89, S 17.04; Found, % C 31.59, H 3.03, N 15.13, S 17.13.

N-Aryl-2-(4-(N-methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetamides (2a-g) (General procedure):

The starting acid **3** (1 g, 4.97 mmol) was suspended in acetone (50 mL), and an equivalent of aniline and dicyclohexylcarbodiimide (1.03 g, 4.49 mmol) were successively added. The reaction mixture was stirred for 2 h. The starting material **3** dissolved and a new precipitate was formed. In the cases of anilines **2g,h**, the precipitate was pure dicyclohexylurea. The mixture was filtrated, the filtrate was evaporated, dried and the residue was crystallized from ethanol. In the other cases, the precipitate was a mixture of the product and dicyclohexylurea, which was filtered off, treated with DMF (20 mL) and the dicyclohexylurea was filtered off.

Then water (70 mL) was added to the filtrate to give product **2** as a solid. This was filtered off and crystallized twice from ethanol.

2-(4-(N-Methyl)carbamoyl-1,2,3-thiadiazol-5-yl)-N-phenylacetamide (2a).

Yield 89%; mp 233-236°C (from ethanol); ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 10.55 (1H, s, NH), 8.85 (1H, q, *J*=5.2 Hz, N*H*Me), 7.8-6.8 (5H, m, Ph), 4.70 (2H, s, C*H*$_2$), 2,87 (3H, d, *J*=5.2 Hz, NHC*H*$_3$); IR (ν_{max}, cm^{-1}): 3300 (NH), 2940 (CH_{arom}), 2940 (CH_{aliph}), 1660 (C=O), 1650 (C=O), 1590, 1530; Anal. calcd. for $C_{12}H_{12}N_4O_2S$, %: C 52.16, H 4.38, N 20.28, S 11.60; Found C 52.33, H 4.41, N 19.99, S 11.61.

2-(4-(N-Methyl)carbamoyl-1,2,3-thiadiazol-5-yl)-N-(4-methylphenyl)acetamide (2b).

Yield 83%; mp 166°C (from ethanol); ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 9.92 (1H, s, NH), 8.9 (1H, q, *J* = 5.2 Hz, N*H*Me), 7.5-7.0 (4H, m, CH_{arom}), 4.72 (2H, s, CH_2), 2,89 (3H, d, *J*=5.2 Hz, NHC*H*$_3$), 2.45 (3H, s, CH_3); IR (ν_{max}, cm^{-1}): 3300 (NH), 3130 (CH_{arom}), 2940 (CH_{aliph}), 1660 (C=O), 1650 (C=O), 1590, 1530; Anal. calcd. for $C_{13}H_{14}N_4O_2S$, %: C 53.78, H 4.86, N 19.30, S 11.04; Found C 53.76, H 4.87, N 19.34, S 11.24.

N-(2-Methoxyphenyl)--(4-(N-methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetamide (2c).

Yield 70%; mp 202-203°C. ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 9.84 (1H, s, NH), 8.90 (1H, q, J=5.2 Hz, N*H*Me), 7.85 (1H, m, CH^o), 7.2-8.8 (3H, m, CH^{m+p+m}), 4.74 (2H, s, CH_2), 3.84 (3H, s, OCH_3), 2.87 (3H, d, J=5.2 Hz, NHC*H*$_3$); IR (ν_{max}, cm^{-1}): 3300 (NH), 2970 (CH_{arom}), 2830 (CH_{aliph}), 1670 (CO), 1645 (CO), 1530, 1490; Anal. calcd. for $C_{13}H_{14}N_4O_3S$, %: C 50.97, H 4.61, N 18.29, S 10,47; Found, % : C 50.84, H 4.62, N 18.54, S 10.44.

N-(4-Methoxyphenyl)-2-(4-(N-methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetamide (2d).

Yield 75%; mp 205-207°C; ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 10.41 (1H, s, NH), 8.91 (1H, q, J=5.2 Hz, N*H*Me), 7.47 (2H, d, J=9.0 Hz, CH^o_{arom}), 6.82 (2H, d, J=9.0 Hz, CH^m_{arom}), 4.67 (2H, s, CH_2), 3.72 (3H, s, OCH_3), 2.87 (3H, d, J=5.2 Hz, NHC*H*$_3$); IR (ν_{max}, cm^{-1}): 3380 (NH), 3060 (CH_{arom}), 2830 (CH_{aliph}), 1670 (C=O), 1645 (C=O), 1550, 1510; Anal. calcd. for $C_{13}H_{14}N_4O_3S$, %: C 50.97, H 4.61, N 18.29, S 10.47; Found, %: C 50.73, H 4.57, N 18.34, S 10.25.

N-(3-Chlorophenyl)-2-(4-(N-methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetamide (2e).

Yield 90%; mp 234-235°C. ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 10.74 (1H, s, NH), 8.91 (1H, q, J=5.2 Hz, N*H*Me), 7.9-7.0 (4H, m, CH_{arom}), 4.72 (2H, s, CH_2), 2.87 (3H, d, J=5.2 Hz, NHC*H*$_3$); IR (ν_{max}, cm^{-1}): 3310 (NH), 3120 (CH_{arom}), 2950 (CH_{aliph}), 1690 (C=O), 1660 (C=O), 1600, 1540; Anal. calcd. for $C_{13}H_{14}N_4O_3S$, %: C 46.38, H 3.57, Cl 11.41, N 18.03, S 10.32; Found, %: C 46.43, H 3.62, Cl 11.67, N 18.17, S 10.28.

N-(4-Chlorophenyl)-2-(4-(N-methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetamide (2f).

Yield 73%; mp 245-247°C; ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 10.75 (1H, s, NH), 8.91 (1H, q, J=5.2 Hz, N*H*Me), 7.72 (2H, d, J=9.0 Hz, CH^o_{arom}), 7.38 (2H, d, J=9.0 Hz, CH^m_{arom}), 4.77 (2H, s, CH_2), 2.92 (3H, d, J=5.2 Hz, NHC*H*$_3$); IR (ν_{max}, cm^{-1}): 3380 (NH), 3120 (CH_{arom}), 2870 (CH_{aliph}), 1670 (CO), 1647 (CO), 1560, 1515; Anal. calcd. for $C_{12}H_{11}ClN_4O_2S$, %: C 46.38, H 3.57, Cl 11.41, N 18.03, S 10.32; Found, %: C 46.45, H 3.54, Cl 11.53, N 18.21, S 10.42.

N-(2,6-Dichlorophenyl)-2-(4-(N-methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetamide (2g).

Yield 16%; mp 229-230°C. ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 10.57 (1H, s, NH), 8.91 (1H, q, J=5.2 Hz, N*H*Me), 7.7-7.2 (3H, m, CH_{arom}), 4.77 (2H, s, CH_2), 2.93 (3H, d, J=5.2 Hz, NHCH_3); IR (ν_{max}, cm^{-1}): 3380 (NH), 3000 (CH_{arom}), 2890 (CH_{aliph}), 1665 (C=O), 1650 (C=O), 1540, 1515; Anal. calcd. for $C_{12}H_{10}Cl_2N_4O_2S$, %: C 41.75, H 2.92, Cl 20.54, N 16.23, S 9.29; Found, %: C 41.53, H 3.04, Cl 20.18, N 16.21, S 9.55.

N-(4-Bromophenyl)-2-(4-(N-methyl)carbamoyl-1,2,3-thiadiazol-5-yl)acetamide (2h).

Yield 67%; mp 234-235°C; ^{1}H NMR (80.13 MHz, DMSO-d_6, δ, ppm): 10.68 (1H, s, NH), 8.92 (1H, q, J=5.2 Hz, N*H*Me), 7.65 (2H, d, J=9.1 Hz, CH^o_{arom}), 7.54 (2H, d, J=9.1 Hz, CH^m_{arom}), 4.71 (2H, s, CH_2), 2.96 (3H, d, J=5.2 Hz, NHCH_3); IR (ν_{max}, cm^{-1}): 3320 (NH), 3010 (CH_{arom}), 2910 (CH_{aliph}), 1660 (CO), 1635 (CO), 1540, 1480; Anal. calcd. for $C_{12}H_{11}BrN_4O_2S$, %: C 40.58, H 3.12, Br 22.50, N 15.77, S 9.03; Found, %: C 40.35, H 3.24, Br 22.06, N 15.37, S 9.31.

5-(1-Aryl-5-hydroxy-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1a-h) (General procedure):

Thiadiazole **2** (5 mmol) was suspended in ethanol (20 mL) and 0.34 g (5 mmol) of sodium ethoxide and 0.915 g (5 mmol) of benzenesulfonyl azide were added at 0°C. The reaction mixture was stirred for 3 h. The sodium salt **1** was collected by filtration and suspended in water. Then a solution of 1 N HCl was added to neutralize the mixture to give product **10** as a solid. It was filtered off and crystallized from toluene.

5-(5-Hydroxy-1-phenyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1a):

Yield 67%; mp 195°C; IR (ν_{max}, cm^{-1}): 3360 (NH), 3060 (CH_{arom}), 2930 (CH_{aliph}), 1635 (C=O), 1590, 1550; Anal. calcd. for $C_{12}H_{10}N_6O_2S$, %: C 47.68, H 3.33, N 27.80, S 10.61; Found, %: C 47.57, H 3.53, N 27.98, S 10.43.

5-(5-Hydroxy-1-(4-methylphenyl)-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1b):

Yield 79%; mp 208-209°C; IR (ν_{max}, cm^{-1}): 3300 (NH), 2930 (CH_{aliph}), 1640 (C=O), 1580, 1500; Anal. calcd. for $C_{13}H_{12}N_6O_2S$, %: C 49.36, H 3.82, N 26.57, S 10.14; Found, %: C 49.27, H 3.58, N 26.42, S 10.14.

(5-Hydroxy-1-(2-methoxyphenyl)-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1c):

Yield 70%; mp 171-173°C; IR (ν_{max}, cm^{-1}): 3370 (NH), 2940 (CH_{arom}), 1640 (C=O), 1580, 1560; Anal. calcd. for $C_{13}H_{12}N_6O_3S$, %: C 46.98, H 3.64, N 25.29, S 9.65; Found, %: C 47.12, H 3.47, N 25.28, S 10.03.

5-(5-Hydroxy-1-(4-methoxyphenyl)-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1d):

Yield 73%; mp 226-228°C; IR (ν_{max}, cm^{-1}): 3330 (NH), 3050 (CH_{arom}), 2840 (CH_{aliph}), 1650 (C=O), 1630, 1530, 1510; Anal. calcd. for $C_{13}H_{12}N_6O_3S$, %: C 46.98, H 3.64, N 25.29, S 9.65; Found, %: C 46.87, H 3.55, N 25.44, S 9.93.

5-(1-(3-Chlorophenyl)-5-hydroxy-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1e):

Yield 71%; mp 180-181°C; IR (ν_{max}, cm^{-1}): 3367 (NH), 3107 (CH_{arom}), 2927 (CH_{aliph}), 1644 (C=O), 1588, 1555; Anal. calcd. for $C_{12}H_9ClN_6O_2S$, %: C 42.80, H 2.69, Cl 10.53, N 24.96, S 9.52; Found, %: C 42.67, H 2.72, Cl 10.71, N 25.14, S 9.72.

5-(1-(4-Chlorophenyl)-5-hydroxy-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1f):

Yield 58%; mp 200-201°C; IR (ν_{max}, cm^{-1}): 3360 (NH), 3150 (CH_{arom}), 2930 (CH_{aliph}), 1650 (C=O), 1580, 1540; Anal. calcd. for $C_{12}H_9ClN_6O_2S$, %: C 42.80, H 2.69, Cl 10.53, N 24.96, S 9.52; Found, %: C 42.75, H 3.01, Cl 10.76, N 25.18, S 9.83.

5-(1-(2,6-Dichlorophenyl)-5-hydroxy-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1g):

Yield 70%; mp 166-167°C; IR (ν_{max}, cm^{-1}): 3330 (NH), 3020 (CH_{arom}), 2870 (CH_{aliph}), 1680 (C=O), 1580, 1550; Anal. calcd. for $C_{12}H_8Cl_2N_6O_2S$, %: C 39.83, H 2.17, Cl 19.10, N 22.64, S 8.64; Found, %: C 39.79, H 2.21, Cl 19.23, N 22.97, S 8.81.

5-(1-(4-Bromophenyl)-5-hydroxy-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-methyl)carboxamide (1h):

Yield 67%; mp 205-206°C; IR (ν_{max}, cm^{-1}): 3360 (NH), 3090 (CH_{arom}), 2940 (CH_{aliph}), 1670 (C=O), 1630, 1560, 1530; Anal. calcd. for $C_{12}H_9BrN_6O_2S$, %: C 37.81, H 2.98, Br 26.98, N 22.05, S 8.41; Found, %: C 37.68, H 3.21, Br 27.16, N 22.35, S 8.71.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-aryl)carboxamides (8a-h) (General procedure):

Procedure A (8c,e,g,h): 0.1 g starting material **1** in 20 mL ethanol was heated at 78°C for 24 h. The product **8** was collected by filtration, washed with ethanol (5 mL) and dried.

Procedure B (8a,b,d,f): 0.1 g starting material **1** in 20 mL DMF was heated at 100°C for 25 h. After addition of water (10 mL) the precipitate **8** was collected by filtration, washed with ethanol (5 mL) and dried.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-phenyl)carboxamide (8a):

Yield 47%; mp 183-185°C; IR (ν_{max}, cm^{-1}): 3570 (NH), 3060 (CH_{arom}), 2920 (CH_{aliph}), 1650 (C=O), 1600, 1550; Anal. calcd. for $C_{12}H_{10}N_6O_2S$, %: C 47.68, H 3.33, N 27.80, S 10.61; Found, %: C 47.75, H 3.24, N 27.83, S 10.51.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)- 1,2,3-thiadiazol-4-(N-(4-methyl)phenyl)carboxamide (8b):

Yield 25%; mp 205-207°C; IR (ν_{max}, cm^{-1}): 3500 (NH), 2920 (CH_{aliph}), 1650 (C=O), 1580, 1530; Anal. calcd. for $C_{13}H_{12}N_6O_2S$, %: C 49.36, H 3.82, N 26.57, S 10.14; Found, %: C 49.41, H 3.58, N 26.67, S 10.21.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-(2-methoxy)phenyl)carboxamide (8c):

Yield 65%; mp 230-232°C; MS: *m/z* 332 [M]; IR (ν_{max}, cm^{-1}): 3340 (NH), 2940 (CH_{arom}), 1650 (C=O), 1600, 1560; Anal. calcd. for $C_{13}H_{12}N_6O_3S$, %: C 46.98, H 3.64, N 25.29, S 9.65; Found, %: C 47.21, H 3.76, N 25.18, S 9.43.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-(4-methoxy)phenyl)carboxamide e (8d):

Yield 42%; mp 204-205°C; IR (ν_{max}, cm^{-1}): 3570 (NH), 3120 (CH_{arom}), 2955 (CH_{aliph}), 1655 (C=O), 1555, 1515; Anal. calcd. for $C_{13}H_{12}N_6O_3S$, %: C 46.98, H 3.64, N 25.29, S 9.65; Found, %: C 46.74, H 3.59, N 25.24, S 9.87.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-(3-chloro)phenyl)carboxamide (8e):

Yield 64%; mp 175°C; IR (ν_{max}, cm^{-1}): 3360 (NH), 3250 (CH_{arom}), 2950 (CH_{aliph}), 1650 (C=O), 1600, 1540; Anal. calcd. for $C_{12}H_9ClN_6O_2S$, %: C 42.80, H 2.69, Cl 10.53, N 24.96, S 9.52; Found, %: C 42.76, H 2.62, Cl 10.66, N 25.24, S 9.42.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-(4-chloro)phenyl)carboxamide (8f):

Yield 68%; mp 234-236°C; IR (ν_{max}, cm^{-1}): 3250 (NH), 3100 (CH_{arom}), 2930 (CH_{aliph}), 1650 (C=O), 1580, 1530; Anal. calcd. for $C_{12}H_9ClN_6O_2S$, %: C 42.80, H 2.69, Cl 10.53, N 24.96, S 9.52; Found, %: C 42.88, H 3.12, Cl 10.46, N 24.87, S 9.63.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-(2,6-dichloro)phenyl)carboxamide (8g):

Yield 62%; mp 243-245°C; IR (ν_{max}, cm^{-1}): 3350 (NH), 3050 (CH_{arom}), 2970 (CH_{aliph}), 1650 (C=O), 1590, 1540; Anal. calcd. for $C_{12}H_8Cl_2N_6O_2S$, %: C 39.83, H 2.17, Cl 19.10, N 22.64, S 8.64; Found, %: C 39.66, H 2.11, Cl 19.32, N 22.77, S 8.51.

5-(5-Hydroxy-1-methyl-1,2,3-triazol-4-yl)-1,2,3-thiadiazol-4-(N-(4-bromo)phenyl)carboxamide (8h):

Yield 23%; mp 238-240°C; IR (ν_{max}, cm^{-1}): 3260 (NH), 3100 (CH_{arom}), 2940 (CH_{aliph}), 1650 (C=O), 1590, 1530; Anal. calcd. for $C_{12}H_9BrN_6O_2S$, %: C 37.81, H 2.98, Br 26.98, N 22.05, S 8.41; Found, %: C 37.65 , H 3.23, Br 26.86, N 22.25, S 8.51.

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