Thia- and Selena-Heterocycles Containing Cycloamidine Substructures: Ring Contraction Reactions of 1,3,4-Thia-/Selenadiazines

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In memoriam to Ariane Beutler (1978 – 2007)

1,3,4-Thia/selena-diazines proved to be suitable starting materials for ring contraction reactions. Treatment with acetic acid/water mixtures leads to highly substituted 1,3,4-thia/selenadiazoles. In addition, the selenadiazoles formed undergo a fast Dimroth-rearrangement to finally yield derivatives of 1,2,4-triazole. The structures of all new derivatives were confirmed by NMR experiments, mass spectroscopy, elemental analysis and X-ray structural analysis.

Key words: Ring Contraction, Dimroth Rearrangement, Triazoles, Thiadiazoles, Selenadiazoles

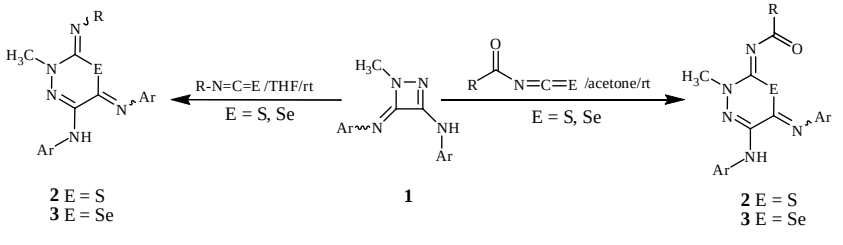
Introduction

Δ^2-1,2-diazetines of type **1** are easily accessible by cyclization reactions of monoalkyl-hydrazines with *bis*-imidoylchlorides of oxalic acid [1]. Such four-membered heterocycles, which contain two nitrogen atoms in the ring positions 1 and 2, are quite rare, and only a few examples were reported. Therefore their application in synthetic chemistry is rather limited [2].

Previously, we showed that due to their inherent ring strain and weak bonds, Δ^2-1,2-diazetines **1** are quite useful in a number of versatile ring transformation reactions [3]. For example, compounds of type **1** react with isothiocyanates and isoselenocyanates in a ring enlargement reaction to yield 1,3,4-thiadiazines **2** and 1,3,4-selenadiazines **3**, respectively, with a wide variability of substitution patterns (Scheme 1) [4].

Being part of the heterocarbonyl systems in derivatives **2** and **3**, the imino substructures allow partial modifications of their backbones. Therefore one aim of our work was the formation of the corresponding oxo derivatives. Due to the different electronic and steric environments of the imino groups, several regioisomers **4**, **5** as well as the dioxo derivatives **6** could be expected [5]. In addition, these functionalities are often the subject of 1,3-acyl rearrangement reactions, finally resulting in derivatives of types **7** and **8**. During the course of our previous research, we have studied such Dimroth rearrangements on different five-membered heterocycles. As an important result we showed that they can be employed in the synthesis of new conjugated thioxo systems [6].

Furthermore, the ring contraction reactions of 1,3,4-thiadiazines **2** are well studied in the literature. The



2 E = S
3 E = Se

1

2 E = S
3 E = Se

Scheme 1. Ringtransformations of 1,2-diazetines **1** to yield 1,3,4-thia(selena)diazines **2**, **3**.

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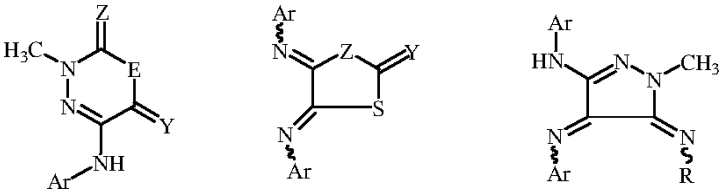


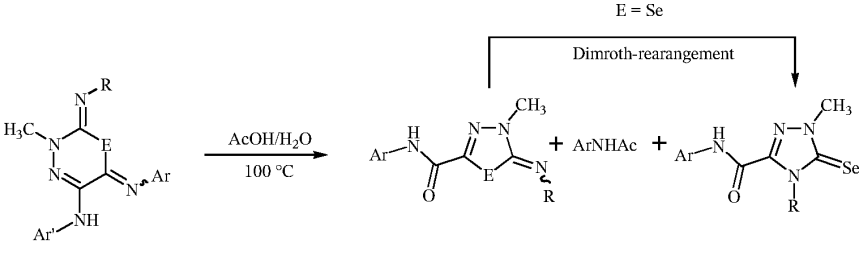
4 E = S/Se, Y = NAr, Z = O
5 E = S/Se, Y = O Z = NR
6 E = S/Se, Y = O Z = O
7 E = NR, Y = NAr, Z = S/Sc
8 E = NAr, Y = S/Sc, Z = NR

9 Y = NR, Z = N-NHMe

10 Y = N-NHMe, Z = NR

11

Scheme 2. Possible products of hydrolysis and ring contraction reactions starting from **2** and **3**.



2/3		**12/13**	**14**	**15**
2a E = S, Ar/Ar′ = Tol,	R = Me	**12a**	E = S, Ar = Tol,	R = Me
2b E = S, Ar/Ar′ = Tol,	R = Et	**12b**	E = S, Ar = Tol,	R = Et
2c E = S, Ar/Ar′ = Tol,	R = Bn	**12c**	E = S, Ar = Tol,	R = Bn
2d E = S, Ar/Ar′ = Tol,	R = PMP	**12d**	E = S, Ar = Tol,	R = PMP
2e E = S, Ar/Ar′ = Tol,	R = Bz	**12e**	E = S, Ar = Tol,	R = Bz
2f E = S, Ar = 4-Br-Ph, Ar′ = Mesityl,	R = 4-^{t}Bu-Ph	**12f**	E = S, Ar = 4-Br-Ph,	R = 4-^{t}Bu-Ph
3a E = Se, Ar/Ar′ = Tol,	R = PMP	**13a/15a**	E = Se, Ar = Tol,	R = PMP
3b E = Se, Ar/Ar′ = Tol,	R = 4-Br-Ph	**13b/15b**	E = Se, Ar = Tol,	R = 4-Br-Ph
3c E = Se, Ar/Ar′ = Tol,	R = 4-^{t}Bu-Ph	**13c/15c**	E = Se, Ar = Tol,	R = 4-^{t}Bu-Ph

Scheme 3. Hydrolysis reaction of heterodiazines **2a – f/3a – c**.

products obtained show a remarkable dependence on the reaction conditions as well as on their substitution patterns [7]. For example, different 1,3-thiazoles were synthesized by the acid-catalyzed hydrolysis of **2** [8]. Similarly, 2-aminothiazoles **9** or thiazolyl-2-hydrazines **10** proved to be possible products in a ring contraction reaction. This useful method was recently employed by Pfeiffer *et al.* in order to make pyrazoles accessible which possess an unusual pattern of substituents [9]. In our case, this protocol should lead to pyrazoles of type **11** allowing further transformations which offer good requirements for the formation of metal chelate complexes (Scheme 2). These heterocycles should be of interest with respect to biological and pharmaceutical applications [10]. However, difficulties in the preparation of such compounds hamper their application.

Results and Discussion

Surprisingly, the hydrolysis reaction of **2** or **3** in acetic acid/water mixtures (10 : 1) did not result in any of the expected products listed in Scheme 2. In a complex reaction, not only the 1,3,4-thia-/selenadiazoles **12/13** were isolated as main products but also the 1,3,4-triazoles **15/16** were formed. Nearly the same product distribution was observed upon treatment of the starting materials **2/3** in glacial acetic acid. The acetylated arylamines **14** were formed as byproducts in equimolar amounts (Scheme 3). The structural assignment shown in Scheme 3 was confirmed by NMR and MS data, elemental analysis and single crystal X-ray structural analysis for the compounds **12b**, **12e**, **13a** and **15a** (Figs. 1 – 3).

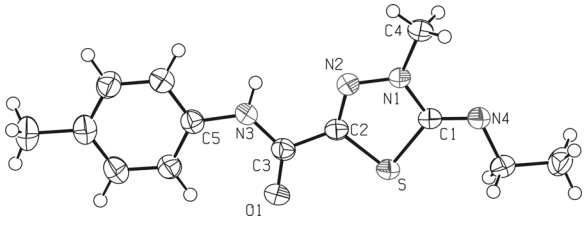


Fig. 1. Molecular structure of derivative **12b** in the solid state as determined by X-ray analysis.

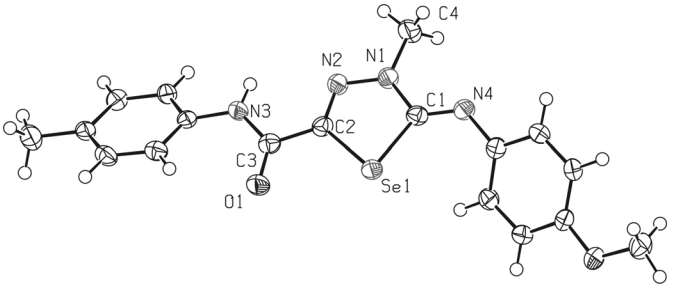


Fig. 2. Molecular structure of derivative **13a** in the solid state as determined by X-ray analysis.

Common synthetic methods to obtain 2-imino-substituted 1,3,4-thia-/selenadiazoles often apply the [2+3]-cycloaddition reaction between hydrazonoyl halides and thio-/selenocarbonyl derivatives [11]. Recently, Firsova *et al.* reported a 2-thioxo-1,3-thiazole as dipolarophile, which strongly limited the variability of substituents at the imino group [11f]. Other authors used carbodithioates and thiocarbamates, respectively, as thioxo components in order to prepare 2-imino-substituted 1,3,4-thiadiazoles [11a – e]. To the best of our knowledge, only one example exists in the literature: the ring contraction reaction of 6-hydroxyimino-tetrahydro-l,3,4-thiadiazine-2-thiones to 3-methyl-5-phenyl-1,3,4-thiadiazole-2(3*H*)-thiones [12]. Analogous ring transformation reactions finally leading to highly substituted 1,3,4-thiadiazoles **12** and 1,3,4-selenadiazoles **13** are unknown.

In order to test the scope and limitations of this mild ring contraction reaction, a variety of aliphatic as well as aromatic substituted thia/selenadiazines was employed. As demonstrated in Scheme 3, this method can be applied to a wide range of substituents at the educts. Due to different electronic and steric effects, the achieved yields and the reaction times differ. In the case of 1,3,4-selenadiazines **3**, a second side reaction was observed. Under the conditions applied for hydrolysis of derivatives **3**, a further product was isolated in a yield of approximately 20 %. The X-ray crystal structural analysis revealed that an additional Dimroth rearrangement leading to 4-aryl-1-methyl-5-selenoxo-1,2,4-triazole-3-carboxamide **15** took place (Scheme 3, Fig. 3). The easy cleavage of the C(2)–Se bond, which is considerably elongated compared to the C(2)–S bond, might be the explanation for this final rearrangement. Similarly, 3-selenoxo-1,2,4-triazoles were obtained by reactions of isoselenocyanates with phenylhydrazines or *S*-methyl-isothiosemicarbazides [13].

Compounds **12/13** are colorless (R = aliphatic) or pale yellow (R = aromatic) crystalline solids that are

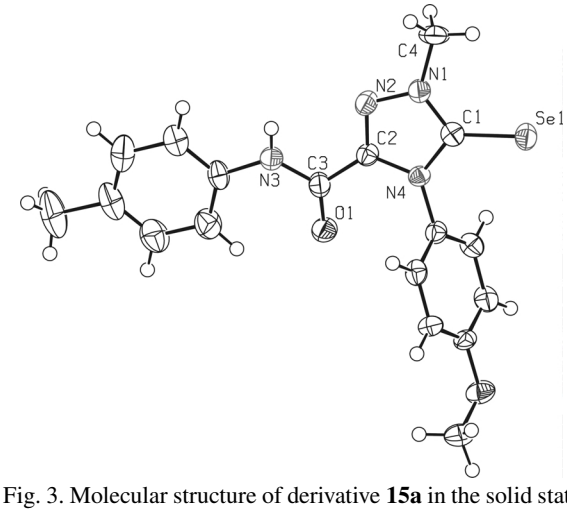
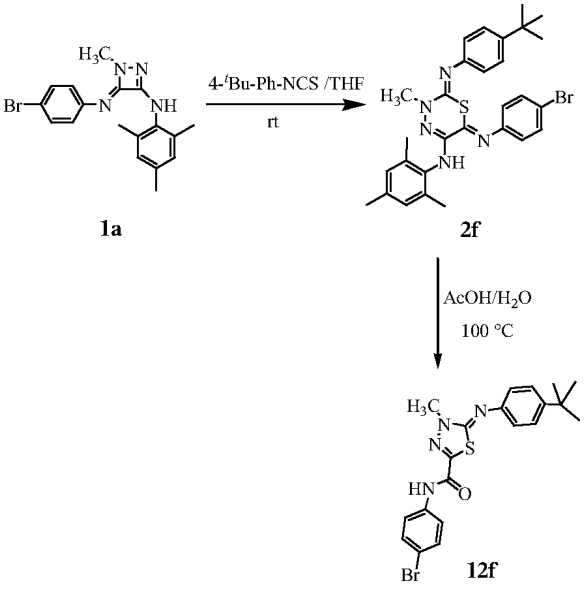


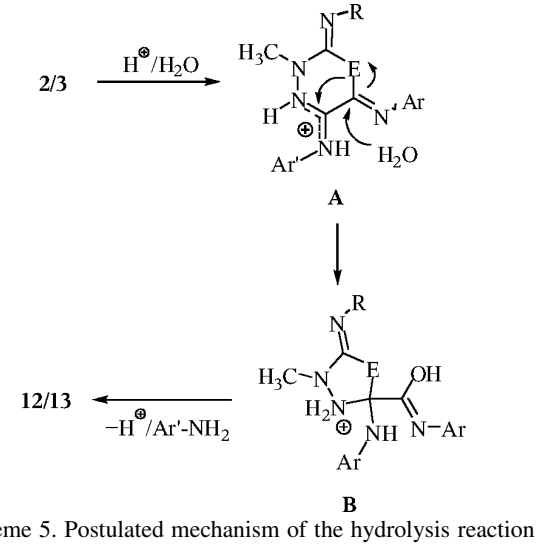
Fig. 3. Molecular structure of derivative **15a** in the solid state as determined by X-ray analysis.

remarkably stable in solution. Even after standing in $CDCl_3$ for a prolonged period, no decomposition of the selenacycles **13** was detected by NMR spectroscopy. In contrast, the selenones **15** decompose by irradiation with UV light under the loss of selenium.

In both **12b** and **13a**, the proton is located at the exocylic atom N(3) and forms a very weak intramolecular hydrogen bond to N(2) [N(2)–H = 2.42 Å (**12b**); 2.39 Å (**13b**)]. The ring bonding angles are significantly influenced by the chalcogen atom. A relatively small C1–E–C2 angle (**12b** = 88.29°; **13b** = 83.83°) is compensated by a widening of the C1–N1–N2 and N2–C2–E angles. The arylamide moiety as well as the imine substituent at N4 show a *cis*-arrangement with respect to the chalcogen atom. The arylamide moiety is slightly twisted out of plane of the heterodiazole substructure. In the ^{13}C NMR spectra, the carbon of the N–C=Se group in **15** resonates at a significantly lower field than the one of the Se–C=N in **13** ($\delta \approx 140$ ppm [**13**], 170 ppm [**15**]). In their ^{77}Se NMR spectra the signals for the selenium nucleus appear at about 500 ppm for **13** and 100 ppm for **15**.



Scheme 4. Regioselective ring transformation reactions of **1a** and **2f**.



Scheme 5. Postulated mechanism of the hydrolysis reaction of heterocycles **2/3**.

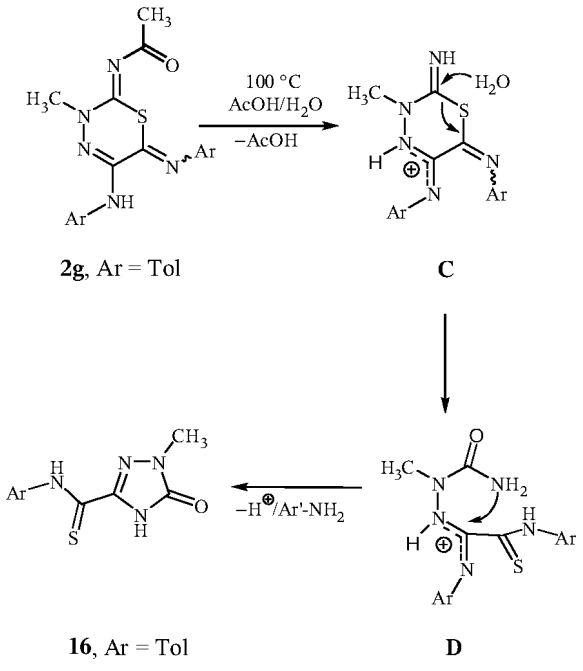
In view of mechanistic investigations for these ring contraction reactions, unsymmetrically substituted Δ^2-1,2-diazetines **1a** with respect to their aromatic substituents (Ar ≠ Ar′) were used. These derivatives could be obtained by a four-step protocol starting from ethyl (chlorocarbonyl) formate and 2,4,6-trimethylbenzenamine. The four-membered ring system of **1a** proved to be unstable and was thus applied directly in the ring transformation reaction with 4-*tert*-butylphenyl isothiocyanate without further purification. The structure of product **2f** was confirmed by NMR and mass spectroscopy, elemental analysis and X-ray structural analysis. The arrangement of substituents in **2f** clearly underlines the regioselectivity of this cycloacylation reaction (Scheme 4).

The hydrolysis reaction of **2f** (Ar ≠ Ar′) resulted in only one product with the 4-bromophenyl substituent (Ar = 4-BrC_6H_4) at the position of the aromatic amide. Consequently, in the course of the hydrolysis, the mesidine moiety is liberated (Ar = 2,4,6-$(CH_3)_3C_6H_2$). This important experimental finding suggests the following mechanism (Scheme 5): First, a protonation reaction under formation of the iminium salt **A** takes place. Due to the existence of amino/imino as well as amidine substructures in the molecules of **2/3**, dynamic protonation and deprotonation equilibria in acidic media exist. The iminium salt **A** can be regarded as a key intermediate in which the chalcogen atom attacks the activated C(5)-position. Then the attack of water at C(6) causes a bond cleavage between C(6) and the chalcogen atom E. The resulting semicyclic aminal **B** is not stable under these conditions and quickly decomposes under acid catalysis into H^+/Ar′-NH_2 and **12** or **13**. The transformation of **13** into **15** can easily be explained by a Dimroth rearrangement reaction which often takes place under acidic catalysis or at higher temperatures. Finally, the eliminated arylamine (Ar′-NH_2) is acetylated to yield derivative **14**.

Generally, the hydrolysis reaction could be applied to acyl-substituted derivatives as shown in example **2e**. However, influenced by the higher electrophilicity of the ring carbon atoms, an increasing number of side reactions was observed. The products and mechanisms of their formation have not yet been fully investigated. For example, no thiadiazole derivatives could be isolated upon hydrolysis of the acetyl derivative **2g** (Scheme 6).

We assume that in this case a desacetylation reaction is the first step which generates the free NH group (**C**) followed by the nucleophilic attack of water and a ring-opening/ring-closure sequence (**D**). The final cyclization product **16**, a derivative of 1,2,4-triazole with an exocyclic thiocarboxamide substructure (Scheme 6), was isolated in about 40 % yield. The result of a single crystal X-ray analysis clearly demonstrated that the NH nitrogen was integrated into the five-membered ring (Fig. 4).

Biological tests of similar compounds such as 3-phenyl-2-*N*-arylimino-2,3-dihydro-1,3,4-thiadiazoles



Scheme 6. Acidic hydrolysis of thiadiazine **2g**.

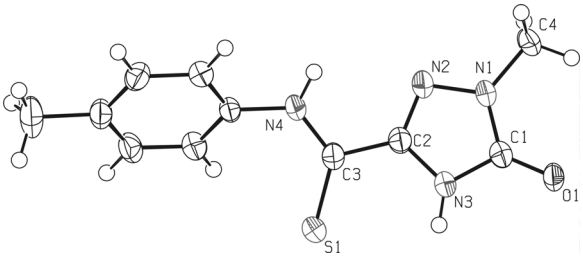


Fig. 4. Molecular structure of derivative **16** in the solid state as determined by X-ray analysis.

[10c] have shown that they exhibit antibacterial and fungicide activity. First biological tests of our compounds showed activity against M. tuberculosis, M. avium und M. kansasii which is similar to that of the reference standard (INH). The modification of these derivatives with respect to new leading structures, especially against resistant bacterial and fungicide strains, will be the subject of further studies.

Conclusions

A new and useful method for the synthesis of 1,3,4-thia-/selenadiazoles **12/13** was presented employing easily accessible heterodiazines **2**, **3** (E = S, Se). In the series of selenacycles, 1,3,4-triazoles of type **15** were isolated as additional products. This new ring contraction method is applicable to a wide range of substituents R as well as Ar in the starting materials. We are currently investigating further ring transformation reactions, especially those of corresponding acyl derivatives. The results will be reported in a forthcoming article.

Experimental Section

All solvents were dried and purified by standard techniques. The reagents employed were of commercial quality (Aldrich, Lancaster, Fluka, Merck). Reactions were monitored by TLC using aluminum plates coated with Al_2O_3 or SiO_2 from Fluka. Melting points were measured with a digital detector system KSPS 1000 from Krüss and with a B-545 (Boetius system) from Büchi and are uncorrected. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AC 250 (250 MHz) or Bruker DRC-400 (400 MHz) spectrometer. ^{77}Se NMR spectra (76 MHz) were obtained on a Bruker DRC-400 spectrometer using Me_2Se as external (^{77}Se) standard. Mass spectra were measured on a spectrometer Trio 2000 from Fisons. Elemental analyses were carried out with an automatic analyzer Varion EL III from Elementar Analysensysteme GmbH.

Crystal structure determinations

Intensity data for the compounds were collected on a Nonius KappaCCD diffractometer using graphite-monochromatized MoK_α radiation. The data were corrected for Lorentz and polarization effects but not for absorption [14, 15]. The structures were solved by Direct Methods (SHELS-97) and refined by full-matrix least-squares methods on F_o^2 (SHELXL-97) [16, 17]. In all cases the hydrogen atom of the amino group N(3) was located in a difference Fourier synthesis and refined isotropically. The other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically. The program XP was used for structure representations [18]. Crystal data and refinement details are summarized in Table 1, selected bond lengths and angles in Table 2.

N^1-(4-Bromo-phenyl)-N^2-mesityl-oxalodiimidoyl dichloride was prepared starting from ethyl (mesitylamino)oxoacetate [19a] which was heated under reflux with 4-bromoaniline in xylene for several days to give the N^1-(4-bromophenyl)-N^2-mesityloxalamide [19b]. The latter was chlorinated following the general protocol [19c] for *bis*-imidoylchlorides (in toluene with phosphorus pentachloride) to give the N^1-(4-bromo-phenyl)-N^2-4-mesityl-oxalodiimidoyl dichloride [19d].

Table 1. Crystal data and refinement details for the X-ray structure determinations.

Compound	**2f**	**12b**	**12e**	**13a**	**15a**	**16**
Formula	$C_{29}H_{32}BrN_5S$	$C_{13}H_{16}N_4OS$	$C_{18}H_{16}N_4O_2S$	$C_{18}H_{18}N_4O_2Se$	$C_{18}H_{18}N_4O_2Se$	$C_{11}H_{12}N_4OS$
M_w, g · mol^{-1}	562.57	276.36	352.41	401.32	401.32	248.31
T, °C	−90(2)	−90(2)	−90(2)	−90(2)	−90(2)	−90(2)
Crystal system	triclinic	monoclinic	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P2_1/n$	$P2_1/c$	$Pbca$
a, Å	9.3843(4)	9.7860(4)	7.9533(3)	8.4055(3)	5.6757(5)	8.8695(3)
b, Å	11.5017(7)	11.7752(4)	20.0780(6)	19.0862(4)	28.302(3)	9.1237(2)
c, Å	13.9601(7)	12.2790(5)	10.5065(4)	10.9646(4)	11.5359(9)	30.2125(8)
α, deg	104.602(2)	90.00	90.00	90.00	90.00	90.00
β, deg	98.079(3)	100.585(2)	94.331(2)	96.430(2)	104.148(5)	90.00
γ, deg	101.403(3)	90.00	90.00	90.00	90.00	90.00
V, Å^3	1400.26(13)	1390.86(9)	1672.95(10)	1747.97(10)	1796.8(3)	2444.88(12)
Z	2	4	4	4	4	8
ρ, g · cm^{-3}	1.334	1.320	1.399	1.525	1.484	1.349
μ, cm^{-1}	15.69	2.31	2.13	21.67	21.09	2.54
Measured data	9917	9182	11808	12217	6761	14828
Data with $I \geq 2\sigma(I)$	4524	2316	2778	3097	2093	1962
Unique data / R_{int}	6347/0.0324	3149/0.0408	3836/0.0427	3986/0.0483	3565/0.0715	2797/0.0620
R_1 [$I \geq 2\sigma(I)$][a]	0.045	0.040	0.047	0.034	0.061	0.045
wR_2 (all data, on F^2)[a]	0.096	0.109	0.127	0.078	0.132	0.123
S[b]	1.008	1.008	1.007	1.005	1.015	1.033
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	0.33/−0.50	0.21/−0.22	0.58/−0.22	0.38/−0.45	0.50/−0.54	0.32/−0.34
CCDC No.[c]	671007	671008	671009	671010	671011	671012

[a] Definition of the R indices: $R_1 = (\Sigma||F_o| - |F_c||)/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ with $w^{-1} = \sigma^2(F_o^2) + (aP)^2$; [b] $S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(N_o - N_p)\}^{1/2}$; [c] CCDC 671007 – 671012 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Selected bond lengths (Å) and angles (deg) for **2**, **12**, **13**, **15** and **16** with estimated standard deviations in parentheses.

Compound	**2f**	**12b**	**12e**	**13a**	**15a**	**16**
	E = S1	E = S	E = S1	E = Se1	E = N4	E = N3
(C1)–(E)	1.780(2)	1.7773(16)	1.7488(19)	1.932(2)	1.374(6)	1.365(2)
(C2)–(E)	1.766(2)	1.7401(17)	1.735(2)	1.879(2)	1.378(6)	1.367(3)
(C2)–(N2)		1.283(2)	1.290(3)	1.281(3)	1.298(6)	1.305(3)
(C1)–(N1)	1.365(3)	1.383(2)	1.355(2)	1.386(3)	1.336(6)	1.359(3)
(C1)–(N4)		1.271(2)	1.308(2)	1.272(3)		
(N1)–(N2)	1.387(3)	1.3573(18)	1.364(2)	1.357(2)	1.375(5)	1.381(2)
(C1)–(Se1)					1.844(5)	
(C1)–(O1)						1.241(2)
(C3)–(S1)						1.650(2)
(C3)–(N2)	1.289(3)					
(C3)–(C2)	1.473(3)					
(C1)–(E)–(C2)	103.17(11)	88.29(8)	87.67(9)	83.83(9)	107.1(4)	107.82(18)
(C1)–(N1)–(N2)	126.93(19)	117.30(13)	117.35(16)	119.64(18)	112.6(4)	112.34(16)
(N2)–(C2)–(Y)		116.28(12)	116.76(14)	116.43(16)	111.3(4)	112.04(17)
(N2)–(C3)–(C2)	126.5(2)					

*1-Methyl-3-(mesitylamino)-4-(4-bromophenylimino)-Δ^2-1,2-diazetine (**1a**)*

A THF solution (30 mL) of the *bis*-imidoyl chloride described above (0.8 g, 2 mmol) and TEA (1.5 mL, 10 mmol) was cooled to 0 °C, and a solution of methylhydrazine (0.11 mL, 2 mmol) in 10 mL of THF was added dropwise. After complete conversion (as monitored by TLC), the reaction mixture was filtered to remove the TEA · HCl and was used without further purification for the following reaction.

*Ring transformation reaction of **1a** with 4-tert-butylphenyl-isothiocyanate to yield 2-(4-tert-butylphenylimino)-6-(4-bromophenylimino)-3,6-dihydro-N-mesityl-3-methyl-2H-1,3,4-thiadiazin-5-amine (**2f**)*

To the cooled THF solution (30 mL) of **1a** (0.74 g, 2 mmol) was added dropwise a solution of 4-*tert*-butylphenyl-isothiocyanate (0.39 g, 2 mmol) in 5 mL of THF. The reaction mixture was warmed up to r. t. and stirred for 6 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (Al_2O_3, chloroform/heptane

2 : 1). Recrystallization from chloroform/heptane gives the heterodiazine **2f** as yellow needles (0.87 g, 77 % yield), m. p. 186.8 – 187.1 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.8 Hz, 2H, CH), 7.29 (d, J = 8.8 Hz, 2H, CH), 6.95 (s, 2H, CH), 6.90 – 6.71 (m, 5H, NH, CH), 3.78 (s, 3H, CH_3N), 2.33, 2.31 (2s, 9H, CH_3), 1.31 (s, 9H, $C(CH_3)_3$). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 146.5, 146.0, 145.4, 144.2, 140.9, 135.8, 135.5, 135.0, 133.6, 132.5, 128.8, 126.2, 121.8, 121.2, 118.9 (C_{aryl}, C_{imin}), 43.5 (CH_3N), 34.3 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 21.0, 18.7 (CH_3). – MS (DEI): m/z = 563 $[M, {}^{81}Br]^+$, 546, 380, 365, 247, 189, 176, 146, 131, 117, 91, 77, 41. – $C_{29}H_{32}BrN_5S$ (562.6): calcd. C 61.91, H 5.73, N 12.45, S 5.70; found C 61.85, H 5.68, N 12.46, S 5.80.

*Hydrolysis reaction of heterodiazines **2a – g** and **3a – c** to yield the heterodiazoles **12a – f/13a – c** and heterotriazoles **15a – c/16***

General procedure

A solution of 1 mmol of the corresponding heterodiazine, 10 mL of glacial acetic acid and 1 mL of water was stirred for approx. 2 h at 100 – 110 °C. After complete conversion (monitored by TLC; Al_2O_3; toluene/acetone 20 : 1), the solvent was removed *in vacuo*, and the residue was purified by column chromatography (Al_2O_3, toluene/acetone 50 : 1). Recrystallization from chloroform/heptane gives heterodiazoles **12/13** and triazoles **15/16**.

*4,5-Dihydro-4-methyl-5-(methylimino)-N-p-tolyl-1,3,4-thiadiazole-2-carboxamide (**12a**)*

This compound was obtained as colorless prisms (150 mg, 57 % yield), m. p. 143 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.28 (s, 1 H, NH), 7.50 (d, J = 8.4 Hz, 2 H, CH), 7.17 (d, J = 8.0 Hz, 2 H, CH), 3.66, 3.09 (2 s, 6 H, CH_3N), 2.34 (s, 3 H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.1, 155.5, 141.9, 134.6, 134.2, 129.7, 119.7 (C_{aryl}, C_{imin}), 43.1, 36.0 (CH_3N), 20.9 (CH_3). – MS (DEI): m/z = 262 $[M]^+$, 174, 146, 133, 106, 102. – $C_{12}H_{14}N_4OS$ (262.3): calcd. C 54.94, H 5.38, N 21.36, S 12.22; found C 54.98, H 5.36, N 21.33, S 12.09.

*5-Ethylimino-4,5-dihydro-4-methyl-N-p-tolyl-1,3,4-thiadiazole-2-carboxamide (**12b**)*

This compound was obtained as colorless prisms (259 mg, 97 % yield), m. p. 129 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1 H, NH), 7.51 (d, J = 8.6 Hz, 2 H, CH), 7.17 (d, J = 8.3 Hz, 2 H, CH), 3.65 (s, 3 H, CH_3N), 3.18 (q, J = 7.3 Hz, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 1.31 (t, J = 7.3 Hz, 3 H, CH_3) – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 155.7, 141.5, 134.5, 134.4, 129.7, 119.7 (C_{aryl}, C_{imin}), 52.2 (CH_2), 35.9 (CH_3N), 20.9, 15.4 (CH_3). – MS (DEI): m/z = 276 $[M]^+$, 261, 174, 160, 146, 133, 106, 91, 69, 56. – $C_{13}H_{16}N_4OS$ (276.4): calcd. C 56.50, H 5.84, N 20.27, S 11.60; found C 56.52, H 5.95, N 20.22, S 11.46.

*5-Benzylimino-4,5-dihydro-4-methyl-N-p-tolyl-1,3,4-thiadiazole-2-carboxamide (**12c**)*

This compound was obtained as colorless prisms (192 mg, 57 % yield), m. p. 140 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.29 (s, 1 H, NH), 7.50 (d, J = 8.4 Hz, 2 H, CH), 7.33 (m, 5 H, CH), 7.18 (d, J = 8.2 Hz, 2 H, CH), 4.37 (s, 2 H, CH_2), 3.73 (s, 3 H, CH_3N), 2.34 (s, 3 H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 158.0, 155.6, 141.6, 139.1, 134.6, 134.3, 129.7, 128.4, 127.6, 127.0, 119.7 (C_{aryl}, C_{imin}), 60.6 (CH_2), 36.0 (CH_3N), 20.9 (CH_3). – MS (DEI): m/z = 338 $[M]^+$, 261, 204, 160, 133, 106, 91, 65, 56. – $C_{18}H_{18}N_4OS$ (338.4): calcd. C 63.88, H 5.36, N 16.56, S 9.47; found C 63.70, H 5.39, N 16.54, S 9.43.

*4,5-Dihydro-4-methyl-5-(4-methoxyphenylimino)-N-p-tolyl-1,3,4-thiadiazole-2-carboxamide (**12d**)*

This compound was obtained as pale yellow prisms (227 mg, 64 % yield), m. p. 109 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.32 (s, 1 H, NH), 7.50 (d, J = 8.4 Hz, 2 H, CH), 7.16 (d, J = 8.2 Hz, 2 H, CH), 7.02 (d, J = 9.2 Hz, 2 H, CH), 6.91 (d, J = 9.2, 2 H, CH), 3.81 (s, 3 H, CH_3O), 3.75 (s, 3 H, CH_3N), 2.33 (s, 3 H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 156.7, 156.3, 155.5, 144.1, 141.5, 134.6, 134.3, 129.7, 121.6, 119.7, 114.9 (C_{aryl}, C_{imin}), 55.5 (CH_3O), 36.2 (CH_3N), 20.9 (CH_3). – MS (DEI): m/z = 354 $[M]^+$, 338, 206, 165, 147, 106, 91, 78, 65. – $C_{18}H_{18}N_4O_2S$ (354.4): calcd. C 61.00, H 5.12, N 15.81, S 9.05; found C 60.95, H 5.06, N 15.69, S 8.75.

*5-Benzoylimino-4,5-dihydro-4-methyl-N-p-tolyl-1,3,4-thiadiazole-2-carboxamide (**12e**)*

This compound was obtained as pale yellow prisms (140 mg, 40 % yield), m. p. 200 °C (dec.). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, NH), 8.32 (m, 2 H, CH), 7.48 (m, 5 H, CH), 7.16 (d, J = 8.2 Hz, 2 H, CH), 4.09 (s, 3 H, CH_3N), 2.32 (s, 3 H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.4, 167.1 (C=O), 155.3, 151.9, 135.5, 135.0, 134.0, 132.4, 129.7, 129.6, 128.2, 119.8 (C_{aryl}, C_{imin}), 38.1 (CH_3N), 20.9 (CH_3). – MS (DEI): m/z = 352 $[M]^+$, 275, 218, 164, 142, 105, 77, 51. – $C_{18}H_{16}N_4O_2S$ (352.4): calcd. C 61.35, H 4.58, N 15.90, S 9.10; found C 61.11, H 4.60, N 15.84, S 9.32.

*5-(4-tert-Butylphenylimino)-4,5-dihydro-4-methyl-N-(4-bromophenyl)-1,3,4-thiadiazole-2-carboxamide (**12f**)*

This compound was obtained as pale yellow needles (285 mg, 64 % yield), m. p. 182.5 – 182.9 °C (dec.). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.37 (s, 1H, NH),

7.60 – 7.30 (m, 6H, CH), 7.02 (d, J = 8.8 Hz, 2H, CH), 3.77 (s, 3H, CH_3N), 1.34 (s, 9H, $C(CH_3)_3$). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 156.3, 155.6, 147.7, 147.2, 141.3, 135.9, 132.2, 126.5, 121.3, 120.0, 117.5 (C_{aryl}, C_{imin}), 36.4 (CH_3N), 34.4 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$). – MS (DEI): m/z = 446 [M, $^{81}Br]^+$, 431, 232, 215, 173, 145, 91, 44, 28. – $C_{20}H_{21}BrN_4OS$ (445.4): calcd. C 53.94, H 4.75, Br 17.94, N 12.58, S 7.20; found C 53.91, H 4.72, Br 18.40, N 12.61, S 7.31.

*4,5-Dihydro-4-methyl-5-(4-methoxyphenylimino)-N-p-tolyl-1,3,4-selenadiazole-2-carboxamide (**13a**)*

This compound was obtained as pale yellow prisms (221 mg, 55 % yield), m. p. 101.6 – 102.8 °C. – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.32 (s, 1H, NH), 7.51 (d, J = 8.4 Hz, 2H, CH), 7.16 (d, J = 8.4 Hz, 2H, CH), 7.06 – 6.88 (m, 4H, CH), 3.81, 3.79 (2s, 6H, CH_3O, CH_3N), 2.33 (s, 3H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 158.8, 157.0, 156.6, 146.0, 143.0, 142.1, 134.5, 134.4, 129.7, 120.9, 119.7, 115.1 (C_{aryl}, C_{imin}), 55.5 (CH_3O), 37.0 (CH_3N), 20.9 (CH_3). – ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 520.4 (s). – MS (DEI): m/z = 402 [M, $^{80}Se]^+$, 385, 254, 213, 162, 147, 133, 121, 106, 91, 77, 28. – $C_{18}H_{18}N_4O_2Se$ (401.3): calcd. C 53.87, H 4.52, N 13.96; found C 53.87, H 4.51, N 13.88.

*5-(4-Bromophenylimino)-4,5dihydro-4-methyl-N-p-tolyl-1,3,4-selenadiazole-2-carboxamide (**13b**)*

This compound was obtained as pale yellow prisms (194 mg, 43 % yield), m. p. 181.5 – 182.3 °C. – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.31 (s, 1H, NH), 7.60 – 7.42 (m, 4H, CH), 7.17 (d, J = 8.2 Hz, 2H, CH), 6.94 (d, J = 8.8 Hz, 2H, CH), 3.81 (s, 3H, CH_3N), 2.34 (s, 3H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.8, 156.7, 151.5, 143.8, 134.6, 134.3, 132.9, 129.7, 121.8, 119.7, 117.3 (C_{aryl}, C_{imin}), 37.1 (CH_3N), 20.9 (CH_3). – ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 526.8 (s). – MS (DEI): m/z = 450 [M, $^{80}Se^{79}Br]^+$, 402, 344, 290, 261, 210, 196, 174, 161, 146, 133, 118, 106, 91, 83, 77, 56, 28. – $C_{17}H_{15}BrN_4OSe$ (450.2): calcd. C 45.35, H 3.36, Br 17.75, N 12.45; found C 45.37, H 3.35, Br 18.40, N 12.59.

*5-(4-tert-Butylphenylimino)-4,5dihydro-4-methyl-N-p-tolyl-1,3,4-selenadiazole-2-carboxamide (**13c**)*

This compound was obtained as pale yellow prisms (286 mg, 67 % yield), m. p. 117.9 – 118.8 °C. – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.34 (s, 1H, NH), 7.52 (d, J = 8.4 Hz, 2H, CH), 7.41 (d, J = 8.6 Hz, 2H, CH), 7.17 (d, J = 8.2 Hz, 2H, CH), 7.01 (d, J = 8.6 Hz, 2H, CH), 3.81 (s, 3H, CH_3N), 2.34 (s, 3H, CH_3), 1.35 (s, 9H, $C(CH_3)_3$). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 158.4, 157.0, 149.7, 147.4, 143.2, 134.5, 134.4, 129.7. 126.7, 119.7, 119.3 (C_{aryl}, C_{imin}), 37.0 (CH_3N), 34.4 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 20.9 (CH_3). – ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 521.2 (s). – MS (DEI): m/z = 428 [M, $^{80}Se]^+$, 413, 224, 206, 173, 158, 145, 133, 117, 106, 91, 77, 65, 28. – $C_{21}H_{24}N_4OSe$ (427.4): calcd. C 59.01, H 5.66, N 13.11; found C 59.09, H 5.73, N 13.19.

*4,5-Dihydro-4-(4-methoxyphenyl)-1-methyl-5-selenoxo-N-p-tolyl-1H-1,2,4-triazole-3-carboxamide (**15a**)*

This compound was obtained as colorless needles (64 mg, 16 % yield), m. p. 233.4 – 234.6 °C (dec.). – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.48 (s, 1H, NH), 7.42 (d, J = 8.6 Hz, 2H, CH), 7.27 (d, J = 8.8 Hz, 2H, CH), 7.12 (d, J = 8.2 Hz, 2H, CH), 7.03 (d, J = 9.0 Hz, 2H, CH), 4.03 (s, 3H, CH_3N), 3.85 (s, 3H, CH_3O), 2.31 (s, 3H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.4 (C=Se), 160.4, 151.6, 144.2, 135.2, 133.7, 129.7, 128.7, 128.2, 119.9, 114.6 (C_{aryl}, C_{imin}), 55.4 (CH_3O), 38.9 (CH_3N), 20.9 (CH_3). – ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 92.3 (s). – MS (DEI): m/z = 402 [M, $^{80}Se]^+$, 387, 360, 314, 296, 290, 268, 227, 213, 188, 161, 147, 133, 108, 91, 82, 77, 59, 44, 28. – $C_{18}H_{18}N_4O_2Se$ (401.3): calcd. C 53.87, H 4.52, N 13.96; found C 53.85, H 4.42, N 13.92.

*4-(4-Bromophenyl)-4,5-dihydro-1-methyl-5-selenoxo-N-p-tolyl-1H-1,2,4-triazole-3-carboxamide (**15b**)*

This compound was obtained as colorless needles (77 mg, 17 % yield), m. p. 245.2 – 246.5 °C (dec.). – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.46 (s, 1H, NH), 7.68 (d, J = 8.6 Hz, 2H, CH), 7.41 (d, J = 8.4 Hz, 2H, CH), 7.24 (d, J = 8.6 Hz, 2H, CH), 7.14 (d, J = 8.4 Hz, 2H, CH), 4.03 (s, 3H, CH_3N), 2.32 (s, 3H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.3 (C=Se), 151.5, 143.7, 134.7, 133.5, 132.7, 129.7, 129.4, 124.4, 112.0 (C_{aryl}, C_{imin}), 38.9 (CH_3N), 20.9 (CH_3). – ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 101.7 (s). – MS (DEI): m/z = 450 [M, $^{80}Se^{79}Br]^+$, 371, 344, 316, 263, 236, 209, 196, 184, 157, 133, 106, 91, 82, 77, 44, 28. – $C_{17}H_{15}BrN_4OSe$ (450.2): calcd. C 45.35, H 3.36, Br 17.75, N 12.45; found C 45.38, H 3.39, Br 17.90, N 12.41.

*4-(4-tert-Butylphenyl)-4,5-dihydro-1-methyl-5-selenoxo-N-p-tolyl-1H-1,2,4-triazole-3-carboxamide (**15c**)*

This compound was obtained as colorless needles (90 mg, 21 % yield), m. p. 225.0 °C (dec.). – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.46 (s, 1H, NH), 7.55 (d, J = 8.4 Hz, 2H, CH), 7.40 (d, J = 8.4 Hz, 2H, CH), 7.28 (d, J = 8.4 Hz, 2H, CH), 7.12 (d, J = 8.4 Hz, 2H, CH), 4.03 (s, 3H, CH_3N), 2.31 (s, 3H, CH_3), 1.37 (s, 9H, $C(CH_3)_3$). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.1 (C=Se), 152.9, 151.7, 144.2, 135.3, 133.7, 133.0, 129.7, 127.0, 126.3, 120.1 (C_{aryl}, C_{imin}), 38.9 (CH_3N), 34.9 ($C(CH_3)_3$), 31.3 ($C(CH_3)_3$), 20.9 (CH_3). – ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 91.7 (s). – MS (DEI): m/z = 428 [M, $^{80}Se]^+$, 413, 322, 306, 294, 278, 238, 214, 199, 187, 173,

159, 133, 106, 91, 82, 77, 65, 28. – $C_{21}H_{24}N_4OSe$ (427.4): calcd. C 59.01, H 5.66, N 13.11; found C 58.99, H 5.75, N 12.99.

*4,5-Dihydro-1-methyl-5-oxo-N-p-tolyl-1H-1,2,4-triazole-3-carbothioamide (**16**)*

This compound was obtained as yellow prisms (109 mg, 44 % yield), m. p. 206 – 210 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.27, 9.89 (2s, 2H, NH), 7.74 (d, J = 8.4 Hz, 2H, CH), 7.24 (d, J = 8.2 Hz, 2H, CH), 3.55 (s, 3H, CH_3N), 2.37 (s, 3H, CH_3). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 175.9 (C=S), 154.3, 142.2, 137.3, 135.2, 129.8, 122.7 (C_{aryl}, C=O, C_{imin}), 32.8 (CH_3N), 21.30 (CH_3). – MS (DEI): m/z = 248 $[M]^+$, 215, 175, 149, 124, 106, 91, 65. – $C_{11}H_{12}N_4OS$ (248.3): calcd. C 53.21, H 4.87, N 22.56, S 12.91; found C 53.10, H 4.80, N 22.52, S 12.95.

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[19] a) O. J.-C. Nicaise, D. M. Mans, A. D. Morrow, E. V. Hefti, E. M. Palkovacs, R. K. Singh, M. A. Zukowska, M. D. Morin, *Tetrahedron* **2003**, *59*, 6433 – 6443; b) ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 10.90, 10.30 (2s, 2 H, NH), 7.86 (d, J = 8.8 Hz, 2 H, CH), 7.55 (d, J = 8.8 Hz, 2 H, CH), 6.91 (s, 2 H, CH), 2.23, 2.11 (2s, 9 H, CH_3); c) R. Bauer, *Ber. Dtsch. Chem. Ges*., **1907**, *40*, 2653; d) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.8 Hz, 2 H, CH), 7.07 (d, J = 8.8 Hz, 2 H, CH), 6.94 (s, 2 H, CH), 2.33, 2.11 (2s, 9 H, CH_3).