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Aqueous microwave-assisted one-pot synthesis of N-substituted rhodanines

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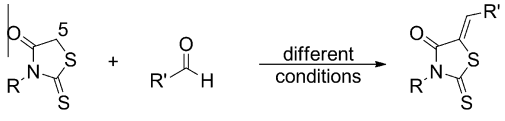
ABSTRACT

Two aqueous, one-pot, microwave-assisted methods for the rapid synthesis of N-substituted rhodanines from amine substrates are described. Alkyl- and benzylamines could be converted into the corresponding rhodanines with an atom-efficient one-pot, three-step protocol based on carbon disulfide and chloroacetic acid in short reaction times and good to excellent yields. An alternative, microwave-assisted one-pot, one-step protocol using bis(carboxymethyl)trithiocarbonate in water was developed for the synthesis of N-arylrhodanines from anilines.

The rhodanine scaffold is a central part of biologically active compounds with various applications and uses.[1–3] In the last years, rhodanines and related heterocycles have been identified as synthetic building blocks and structural scaffolds that possess a unique biomolecular interaction profile.[3–5] N-Substituted 5-arylidenerhodanines such as the aldose reductase inhibitor epalrestat are, for example, used in the treatment of diabetic neuropathy[6] or evaluated as selective HCV protease inhibitors.[7] Additional applications are in analytical chemistry, such as the amperometric determination of heavy metal ions.[8] For the discovery of new lead structures in drug discovery or agricultural chemistry, based on high throughput screening, synthetic methods are required which deliver highly diverse derivatives in a timely manner. Under these circumstances, multicomponent microwave-assisted chemistry appears to be a promising synthetic method.[9]

The synthetic approach toward N-substituted 5-arylidenerhodanines is usually based on a Knoevenagel condensation of the N-substituted rhodanine with aromatic or aliphatic aldehydes (Scheme 1). For this reaction, numerous microwave-based approaches are known,[5,10–12] whereas, to our knowledge, no straightforward synthesis of the N-substituted rhodanine precursors with a 'free' 5-position has been described yet. Because only a small number of these N-substituted rhodanine synthons are commercially available, there is a clear requirement for a straightforward synthetic approach to make these key building blocks available for drug discovery and related settings.



Scheme 1. General synthetic approach for N-substituted 5-arylidenerhodanines.

Radi et al. recently described a microwave-assisted one-pot, two-step protocol to N-substituted 5-arylidenerhodanines in dimethoxyethane with various amine substrates and yields between 31% and 64%.[11] This method is based on the bis(carboxymethyl)trithiocarbonate reagent, which is commercially available, but more expensive and less atom-efficient than alternative synthetic reagents. For example, carbon disulfide is an excellent alternative which can be used in efficient syntheses of rhodanine derivatives. Multicomponent, one-pot syntheses of rhodanines using carbon disulfide have been reported for the direct synthesis of highly substituted rhodanines by various authors, but these methods are usually inadequate for the synthesis of N-substituted rhodanines without substitution at position 5,[13–16] and therefore do not yield products that offer the desired synthetic 'freedom to operate' in 5-position. Tissaoui et al. recently described an 'electrogenerated base-promoted' synthesis of several *N*-benzylrhodanine derivatives.[17] Older protocols for N-substituted rhodanines require long reaction times under aqueous conditions.[18] Considering the latter aspect, we reasoned that aqueous microwave assisted chemistry might be an interesting approach for the synthesis of rhodanine derivatives under environmentally gentle conditions.[19]

Herein we report two aqueous, microwave-assisted, one-pot protocols for the rapid and efficient synthesis of N-substituted rhodanines based on either carbon disulfide or the bis(carboxymethyl)trithiocarbonate reagent. These protocols enable the

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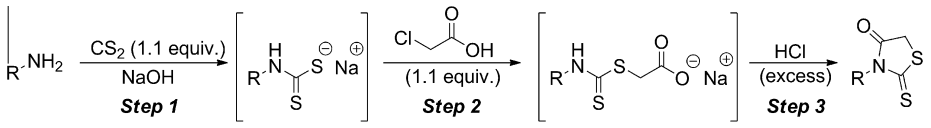


Scheme 2. One-pot, three-step approach for the synthesis of N-substituted rhodanines.

synthesis of a large number of N-substituted rhodanines from the corresponding amines under environmentally friendly conditions. As a highly atom-efficient approach we first evaluated a three-component reaction of the amine with carbon disulfide and chloroacetic acid. Only one equivalent hydrogen chloride and water are lost with this approach (Scheme 2). The reaction has been described for several substrates and under different conditions,[18,20,21] but a refluxing/stirring procedure and extended reaction times are required for most of them, reducing their usefulness for a high throughput synthetic approach. Our procedure employs sodium hydroxide as the reagent in the first two reaction steps and hydrogen chloride in the final reaction step, as described recently for amino acid substrates.[21] After some optimization steps with benzylamine as a model substrate, we identified the conditions for a one-pot, three-step synthetic approach shown in Table 1 (entries 1 and 4) as starting point for further investigations. Benzylamine and carbon disulfide are reacted in water or ethanol under basic conditions in a microwave reactor for 5 min at 100 °C, followed by the addition of chloroacetic acid and a second reaction for 5 min at 100 °C. Afterwards, an excess of aqueous hydrochloric acid is added and a final reaction step is executed at 120 °C for 30 min at pressures around 10 bar. Higher temperatures accompanied by shorter reaction times lead to complex reaction profiles and higher pressures, which can become difficult to control. For benzylamine, ethanol was identified as a more suitable solvent than water. The reaction in ethanol leads to an isolated yield of 81% (Table 1, entry 1) instead of 61% with the same procedure in water (Table 1, entry 4). The addition of sodium hydroxide in the first step serves to support the nucleophilic attack of the amine at carbon disulfide. If the base was omitted, the isolated yield dropped to 38% (Table 1, entry 2). The longer reaction time in the third step is necessary to obtain high yields: Reduction from 30 to 5 min at 120 °C resulted in a yield of 32% (Table 1, entry 3). Different non-microwave-assisted conditions for a methodological comparison are also reported (Table 1, entries 5–9). In correlation with the previously discussed microwave-assisted variants the use of ethanol as the solvent leads to higher yields (45–59%) compared to water (38%). However, the yield of the optimized microwave-assisted protocol in ethanol with 81% could not be achieved, even when very long reaction times were used (Table 1, entry 9). Nevertheless these protocols might be useful alternatives for the synthesis of N-substituted rhodanines if a microwave-assisted approach could not be applied.

With the conditions shown in Table 1, entry 1 and Table 1, entry 4, respectively, we investigated several amine substrates listed in Table 2. Water instead of ethanol was used as the solvent for all reactions with amines except the benzylamine derivatives, because higher yields and cleaner reaction profiles were observed. Although many products precipitated in water or were easily separable as oils, a chromatographic purification was executed for all derivatives to obtain a reliable basis for yield comparisons. The aliphatic derivatives **1**–**10** show yields in a range of 58–77% with good reaction profiles. The yield for the benzylamine derivatives **11**–**14** depends on the electronic properties of the used aromatic substituent. Compounds **11**–**13** with lower electron density in the aromatic system were obtained in higher yields than the electron-rich derivative **14**. Using *para*-toluidine as a model substrate for aryl amines under different conditions, including attempts that involved the isolation of intermediate ammonium salts,[18,20,22] we were unable to isolate the desired rhodanine **15** from byproducts and found only minute amounts of the product. For the aryl derivatives **16** and **17**, improved reaction profiles and higher, albeit not satisfying yields could be observed. Some amines shown in Figure 1(A) could not be converted into the corresponding rhodanine derivatives using the method described above. *tert*-Butylamine and ethanolamine were the only two tested classical aliphatic substrates which did not react in the expected way. The *N*-*tert*-butylrhodanine is not yet described in the literature and may be highly prone to elimination of butene. Although the reaction of glycine and other amino acids is described for similar reaction conditions,[21] we were not able to convert this protocol to a microwave assisted variant.

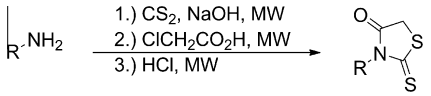
Considering the inferior results for the arylamines and other problematic substrates, an alternative one-pot, one-step protocol based on the bis(carboxymethyl)trithiocarbonate reagent was evaluated. There are also several protocols for this reaction, primarily for arylamine substrates, described in the literature. Some of these protocols require organic solvents with different additional reagents,[11,23] whereas alternative protocols are performed under aqueous conditions without any further catalytic component.[10,18] We developed a straightforward and time-saving microwave-assisted approach for the latter conditions. Again, *para*-toluidine was evaluated as a model substrate for reactions with bis(carboxymethyl)trithiocarbonate in water at different time and temperature conditions (Table 3, entries 1–5). Under non-microwave-assisted, refluxing conditions (180 min, water), the isolated yield of pure

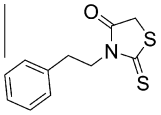
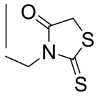
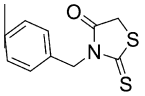
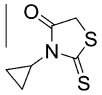
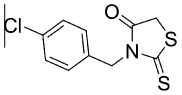
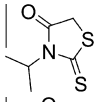
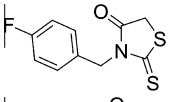
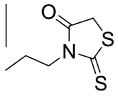
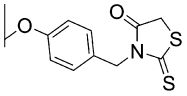
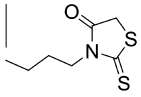
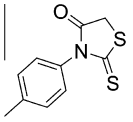
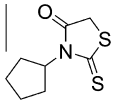
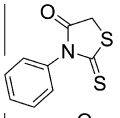
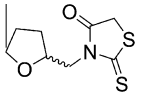
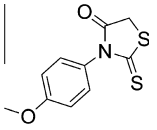
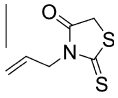
Table 1
Evaluation of conditions for the synthesis of the model compound *N*-benzylrhodanine (**11**)

Entry	Solvent	Step 1			Step 2			Step 3			Yield[a] (%)
		Conditions	Time	Equiv. NaOH	Conditions	Time	Equiv. NaOH	Conditions	Time	Conc. HCl (ml)	
1	EtOH	MW: 100 °C	5 min	2.2	MW: 100 °C	5 min	0	MW: 120 °C	30 min	3	81
2	EtOH	MW: 100 °C	5 min	0	MW: 100 °C	5 min	1.05	MW: 120 °C	30 min	3	38
3	EtOH	MW: 100 °C	5 min	2.2	MW: 100 °C	5 min	0	MW: 120 °C	5 min	3	32
4	H_2O	MW: 100 °C	5 min	2.2	MW: 100 °C	5 min	0	MW: 120 °C	30 min	3	61
5	EtOH	Δ: reflux	10 min	2.2	Δ: reflux	10 min	0	Δ: reflux	60 min	3	59
6	EtOH	Δ: reflux	30 min	2.2	Δ: reflux	30 min	0	Δ: reflux	90 min	3	45
7	H_2O	Δ: reflux	10 min	2.2	Δ: reflux	10 min	0	Δ: reflux	60 min	3	38
8	H_2O	Δ: reflux	30 min	2.2	Δ: reflux	30 min	0	Δ: reflux	90 min	3	38
9	EtOH	Room temp.	3 h	2.2	Room temp.	3 h	0	Δ: reflux	18 h	3	55

[a] Isolated yield after workup and chromatographic purification.

Table 2
Microwave-assisted synthesis of N-substituted rhodanines: (1) amine (10 mmol), NaOH (22 mmol), CS_2 (11 mmol), solvent (10 ml), 100 °C, 5 min, (2) $ClCH_2CO_2H$ (11 mmol), 100 °C, 5 min, (3) HCl (3 ml), 120 °C, 30 min[24]



Compound	Structure	Solvent[a]	Yield[b] (%)	Compound	Structure	Solvent[a]	Yield[b] (%)
1[c]		H_2O	69	**10**[e]		H_2O	65
2[d]		H_2O	71	**11**		EtOH	81
3		H_2O	65	**12**		EtOH	80
4		H_2O	69	**13**		EtOH	85
5		H_2O	58	**14**		EtOH	20
6		H_2O	58	**15**		H_2O	<5[f]
7		H_2O	59	**16**		H_2O	13
8		H_2O	68	**17**		H_2O	19
9		H_2O	77				

[a] Solvent for step 1 and step 2. In step 3 aqueous HCl was added.
[b] Isolated yield after workup and chromatographic purification unless indicated otherwise.
[c] The amine was added as a 33% solution in EtOH.
[d] The amine was added as a 70% solution in H_2O.
[e] The amine was added as the hydrochloride along with one additional equivalent of NaOH.
[f] Compound could not be isolated but was detected by NMR and mass spectrometry.

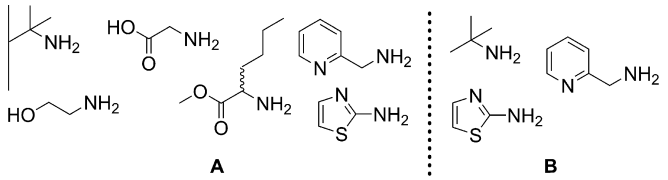


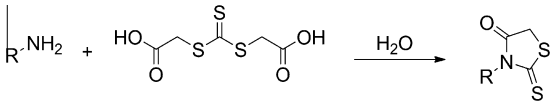
Figure 1. (A) Amines which could not be converted to the N-rhodanine derivative using the carbon disulfide-based method (Table 2). (B) Amines which could not be converted to the N-rhodanine derivative using the bis(carboxymethyl)trithiocarbonate method (Table 3).

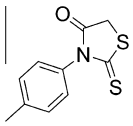
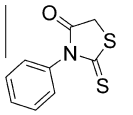
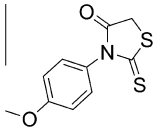
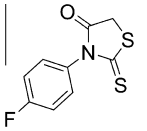
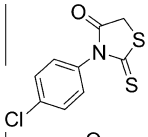
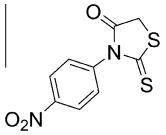
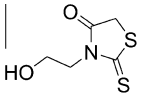
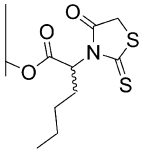
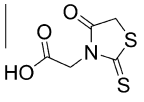
compound **15** was less satisfactory than previously reported.[10] Using the microwave assisted approaches shown in entries 2–4 (Table 3) at 120 °C and 160 °C, compound **15** could not be isolated in high purity. Under microwave conditions at 160 °C for 15 min, a cleaner product could be isolated in a yield of 54% (Table 3, entry 5). These conditions were used for most of the following derivatives listed in Table 3. The *para*-methoxy (**17**), *para*-fluoro (**18**), *para*-chloro (**19**), and *N*-phenyl (**16**) derivatives could be isolated in yields between 32% and 47%. The reactivity of *para*-nitroaniline was very low: Nearly all amine substrate was recovered, and a small amount of compound **20** was isolated in good purity and a yield of 3%.

In contrast to the first method, ethanolamine could be transformed into the corresponding rhodanine derivative **21** in low yields, independent of the reaction time. A similar observation was made for the racemic norleucine methyl ester derivative **22**. Using glycine, we could detect the desired product (**23**) after purification, but were unable to isolate it from a complex mixture of byproducts. However, alternative methods have been described for amino acid substrates.[21]

The yields for N-arylrhodanines with the second method were found to be much higher in comparison to the carbon disulfide-meth-

Table 3
Microwave-assisted synthesis of N-substituted rhodanines using 1.1 equiv bis(carboxymethyl)trithiocarbonate in water: amine (10 mmol), bis(carboxymethyl)trithiocarbonate (11 mmol), and H_2O (10 ml)[25]



Entry	Compound	Structure	Conditions	Yield[a] (%)
1			Δ: reflux, 180 min	46
2			MW: 120 °C, 10 min	49[b]
3	**15**		MW: 120 °C, 90 min	68[b]
4			MW: 160 °C, 5 min	60[b]
5			MW: 160 °C, 15 min	54
6	**16**		MW: 160 °C, 15 min	32
7	**17**		MW: 160 °C, 15 min	39
8	**18**		MW: 160 °C, 5 min	15
			MW: 160 °C, 15 min	38
9				
10	**19**		MW: 160 °C, 15 min	47
11	**20**		MW: 160 °C, 15 min	3
12	**21**		MW: 160 °C, 5 min	17
13			MW: 160 °C, 15 min	16
14	**22**[c]		MW: 160 °C, 15 min	15
15	**23**[d]		MW: 160 °C, 15 min	<5[e]

[a] Isolated yield after workup and chromatographic purification unless indicated otherwise.
[b] A small amount of impurity could not be fully separated by standard chromatographic procedures.
[c] The amine was added as the hydrochloride salt along with one additional equivalent of NaOH.
[d] 1 equiv of NaOH was added.
[e] Compound could not be isolated but was detected by NMR and mass spectrometry.

od. However, not all amines could be converted into their rhodanine derivatives with the second method (Fig. 1B): 2-Aminothiazole, *tert*-butylamine, and 2-picolylamine gave no product after 15 min at 160 °C. N-Arylrhodanines are probably better obtained by protocols that involve a base catalyst or other additional reagents.[11,23]

In summary, we present two straightforward protocols for the rapid synthesis of N-substituted rhodanine derivatives that do not carry additional substituents in the highly reactive position 5 and are thus valuable synthons to obtain rhodanine derivatives with the molecular complexity and diversity that are required in drug-discovery and related settings. Numerous substrates can be converted using these protocols in high yields. The first protocol can preferentially be applied to alkyl- and benzylamine substrates, and the second for arylamine substrates. Further improvements to this method can be envisaged for the second method and for the use of arylamine substrates.

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References and notes

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24. General procedure for the synthesis of N-substituted rhodanines using the carbon disulfide based method: a suspension of amine (10 mmol), sodium hydroxide (22 mmol), and carbon disulfide (11 mmol) in the given solvent (10 ml) was reacted in a microwave reactor (Monowave 300, Anton Paar) for 5 min at 100 °C. After automated cooling to 40 °C chloroacetic acid (11 mmol) was added and the mixture was reacted again at 100 °C for 5 min. After cooling (40 °C) concentrated hydrochloric acid (3 ml) was added and the reaction was finished at 120 °C for 30 min. The crude product was extracted with ethyl acetate (if ethanol was used as the solvent water was added before extraction) and purified by flash chromatography (cyclohexane/ethyl acetate) using a Biotage Isolera One system.
3-Methyl-2-thioxo-1,3-thiazolidin-4-one (**1**): Pale yellow solid (69% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.37 (s, 3H), 3.99 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.3, 35.6, 173.7, 201.3 ppm; MS (EI, 70 eV): *m/z* (%): 147.0 (100) [M^+]; Anal. Calcd for $C_4H_5NOS_2$: C, 32.63; H, 3.42; N, 9.51. Found: C, 32.63; H, 3.57; N, 9.40.
3-Ethyl-2-thioxo-1,3-thiazolidin-4-one (**2**): Pale yellow solid (71% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 3H), 3.95 (s, 2H), 4.05 (q, *J* = 7.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 35.4, 39.9, 173.6, 200.9 ppm; MS (EI, 70 eV): *m/z* (%): 161.0 (95) [M^+]; Anal. Calcd for $C_5H_7NOS_2$: C, 37.24; H, 4.38; N, 8.69. Found: C, 37.33; H, 4.51; N, 8.68.
3-Cyclopropyl-2-thioxo-1,3-thiazolidin-4-one (**3**): Colorless solid (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (m, 2H), 1.12 (m, 2H), 2.72 (m, 1H), 3.89 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.2, 27.6, 35.1, 174.0, 202.3 ppm; MS (EI, 70 eV): *m/z* (%): 173.0 (95) [M^+]; Anal. Calcd for $C_6H_7NOS_2$: C, 41.59; H, 4.07; N, 8.08. Found: C, 41.65; H, 4.22; N, 8.05.

3-Isopropyl-2-thioxo-1,3-thiazolidin-4-one (**4**): Pale yellow solid (69% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, J = 6.9 Hz, 6H), 3.82 (s, 2H), 5.22 (sept, J = 6.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 34.0, 50.4, 174.2, 202.1 ppm; MS (EI, 70 eV): m/z (%): 175.0 (93) [M^+]; Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; N, 7.99. Found: C, 41.26; H, 5.25; N, 7.99.

3-Propyl-2-thioxo-1,3-thiazolidin-4-one (**5**): Yellow liquid (58% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.4 Hz, 3H), 1.66 (m, 2H), 3.93 (m, 2H), 3.96 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 20.1, 35.3, 46.2, 173.9, 201.2 ppm; MS (EI, 70 eV): m/z (%): 175.0 (100) [M^+]; Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; N, 7.99. Found: C, 41.04; H, 5.22; N, 8.36.

3-Butyl-2-thioxo-1,3-thiazolidin-4-one (**6**): Yellow liquid (58% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.3 Hz, 3H), 1.35 (m, 2H), 1.61 (m, 2H), 3.95 (s, 2H), 3.97 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 20.0, 28.8, 35.3, 44.6, 173.9, 201.2 ppm; MS (EI, 70 eV): m/z (%): 189.0 (100) [M^+]; Anal. Calcd for $C_7H_{11}NOS_2$: C, 44.41; H, 5.86; N, 7.40. Found: C, 44.59; H, 5.78; N, 8.05.

3-Cyclopentyl-2-thioxo-1,3-thiazolidin-4-one (**7**): Colorless solid (59% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53–1.67 (m, 2H), 1.80–2.00 (m, 4H), 2.03–2.17 (m, 2H), 3.81 (s, 2H), 5.31 (quint, J = 8.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 27.5, 34.2, 57.8, 173.8, 202.5 ppm; MS (EI, 70 eV): m/z (%): 201.0 (76) [M^+]; Anal. Calcd for $C_8H_{11}NOS_2$: C, 47.73; H, 5.51; N, 6.96. Found: C, 47.73; H, 5.58; N, 6.97.

3-(Tetrahydrofuran-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one (**8**): Pale yellow solid (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (m, 1H), 1.80–2.07 (m, 3H), 3.72 (m, 1H), 3.82–3.95 (m, 2H), 3.98 (d, J = 3.8 Hz, 2H), 4.09 (m, 1H), 4.36 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 29.1, 35.3, 47.9, 67.9, 74.6, 173.9, 201.6 ppm; MS (EI, 70 eV): m/z (%): 217.0 (18) [M^+]; Anal. Calcd for $C_8H_{11}NO_2S_2$: C, 44.22; H, 5.10; N, 6.45. Found: C, 44.53; H, 5.24; N, 6.39.

3-Allyl-2-thioxo-1,3-thiazolidin-4-one (**9**): Pale yellow solid (77% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 2H), 4.57 (dt, J = 6.0, 1.4 Hz, 2H), 5.18–5.28 (m, 2H), 5.77 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.7, 46.4, 119.5, 129.3, 173.3, 200.6 ppm; MS (EI, 70 eV): m/z (%): 173.1 (96) [M^+]; Anal. Calcd for $C_6H_7NOS_2$: C, 41.59; H, 4.07; N, 8.08. Found: C, 41.66; H, 3.98; N, 8.05.

3-(2-Phenylethyl)-2-thioxo-1,3-thiazolidin-4-one (**10**): Pale yellow solid (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.93 (m, 2H), 3.92 (s, 2H), 4.19 (m, 2H), 7.20–7.33 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.6, 35.2, 45.7, 126.8, 128.5, 128.9, 137.3, 173.4, 200.9 ppm; MS (EI, 70 eV): m/z (%): 236.9 (76) [M^+]; Anal. Calcd for $C_{11}H_{11}NOS_2$: C, 55.67; H, 4.67; N, 5.90. Found: C, 55.67; H, 4.82; N, 5.88.

3-Benzyl-2-thioxo-1,3-thiazolidin-4-one (**11**): Pale yellow solid (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 2H), 5.18 (s, 2H), 7.30 (m, 3H), 7.42 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4, 47.6, 128.2, 128.6, 129.0, 134.7, 173.8, 201.0 ppm; MS (EI, 70 eV): m/z (%): 222.9 (88) [M^+]; Anal. Calcd for $C_{10}H_9NOS_2$: C, 53.78; H, 4.06; N, 6.27. Found: C, 53.92; H, 4.13; N, 6.23.

3-(4-Chlorobenzyl)-2-thioxo-1,3-thiazolidin-4-one (**12**): Pale yellow solid (80% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 2H), 5.13 (s, 2H), 7.27 (m, 2H), 7.38 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.6, 46.9, 128.7, 130.6, 133.1, 134.2, 173.7, 200.8 ppm; MS (EI, 70 eV): m/z (%): 256.8 (85) [M^+]; Anal. Calcd for $C_{10}H_8ClNOS_2$: C, 46.60; H, 3.13; N, 5.43. Found: C, 46.48; H, 3.43; N, 5.23.

3-(4-Fluorobenzyl)-2-thioxo-1,3-thiazolidin-4-one (**13**): Pale yellow solid (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 2H), 5.14 (s, 2H), 6.98 (m, 2H), 7.44 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4, 46.8, 115.3 + 115.6 (d, J_{CF} = 21.6 Hz), 130.5 + 130.6 (d, J_{CF} = 3.5 Hz), 131.1 + 131.3 (d, J_{CF} = 8.1 Hz), 160.9 + 164.2 (d, J_{CF} = 247 Hz), 173.8, 200.9 ppm; MS (EI, 70 eV): m/z (%): 240.9 (84) [M^+]; Anal. Calcd for $C_{10}H_8FNOS_2$: C, 49.77; H, 3.34; N, 5.80. Found: C, 50.30; H, 3.71; N, 5.38.

3-(4-Methoxybenzyl)-2-thioxo-1,3-thiazolidin-4-one (**14**): Pale yellow solid (20% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H), 3.95 (s, 2H), 5.11 (s, 2H), 6.83 (m, 2H), 7.41 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4, 47.1, 55.2, 113.8, 127.0, 130.8, 159.5, 173.9, 201.0 ppm; MS (EI, 70 eV): m/z (%): 252.9 (81) [M^+]; Anal. Calcd for $C_{11}H_{11}NO_2S_2$: C, 52.15; H, 4.38; N, 5.53. Found: C, 53.78; H, 4.88; N, 5.04.

25. General procedure for the synthesis of N-substituted rhodanines using the bis(carboxymethyl)trithiocarbonate based method: A suspension of amine (5 mmol) and bis(carboxymethyl)trithiocarbonate (5.5 mmol) in water was reacted in a microwave reactor (Monowave 300, Anton Paar) at the different described time and temperature conditions. After automated cooling to 40 °C the crude product was extracted with ethyl acetate and purified by flash chromatography (cyclohexane/ethyl acetate) using a Biotage Isolera One system.

3-(4-Methylphenyl)-2-thioxo-1,3-thiazolidin-4-one (**15**): Pale yellow solid (54% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 4.17 (s, 2H), 7.07 (m, 2H), 7.33 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 36.3, 128.0, 130.4, 132.2, 140.0, 173.5, 201.3 ppm; MS (EI, 70 eV): m/z (%): 223.1 (100) [M^+]; Anal. Calcd for $C_{10}H_9NOS_2$: C, 53.78; H, 4.06; N, 6.27. Found: C, 55.92; H, 4.28; N, 6.84.

3-Phenyl-2-thioxo-1,3-thiazolidin-4-one (**16**): Pale yellow solid (32% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.18 (s, 2H), 7.19 (m, 2H), 7.52 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.3, 128.3, 129.6, 129.8, 134.9, 173.4, 201.1 ppm; MS (EI, 70 eV): m/z (%): 208.9 (100) [M^+]; Anal. Calcd for $C_9H_7NOS_2$: C, 51.65; H, 3.37; N, 6.69. Found: C, 50.51; H, 3.42; N, 6.33.

3-(4-Methoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one (**17**): Pale yellow solid (39% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3H), 4.16 (s, 2H), 7.02 (m, 2H), 7.10 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2, 55.5, 114.9, 127.2, 129.4, 160.3, 173.5, 201.5 ppm; MS (EI, 70 eV): m/z (%): 238.9 (100) [M^+]; Anal. Calcd for $C_{10}H_9NO_2S_2$: C, 50.19; H, 3.79; N, 5.85. Found: C, 50.24; H, 3.73; N, 5.82.

3-(4-Fluorophenyl)-2-thioxo-1,3-thiazolidin-4-one (**18**): Pale yellow solid (38% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.18 (s, 2H), 7.15–7.25 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2, 116.6 + 116.9 (d, J_{CF} = 23.3 Hz), 130.2 + 130.4 (d, J_{CF} = 9.2 Hz), 130.5 + 130.6 (d, J_{CF} = 3.2 Hz), 161.3 + 164.6 (d, J_{CF} = 250 Hz), 173.3, 201.0 ppm; MS (EI, 70 eV): m/z (%): 227.1 (100) [M^+]; Anal. Calcd for $C_9H_6FNOS_2$: C, 47.56; H, 2.66; N, 6.16. Found: C, 47.68; H, 2.41; N, 6.17.

3-(4-Chlorophenyl)-2-thioxo-1,3-thiazolidin-4-one (**19**): Pale yellow solid (47% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.18 (s, 2H), 7.14 (m, 2H), 7.50 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.3, 129.7, 129.9, 133.1, 135.8, 173.1, 200.7 ppm; MS (EI, 70 eV): m/z (%): 242.9 (100) [M^+]; Anal. Calcd for $C_9H_6ClNOS_2$: C, 44.35; H, 2.48; N, 5.75. Found: C, 45.76; H, 2.51; N, 6.23.

3-(4-Nitrophenyl)-2-thioxo-1,3-thiazolidin-4-one (**20**): Pale yellow solid (3% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (s, 2H), 7.43 (m, 2H), 8.39 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.5, 124.8, 129.9, 140.1, 148.2, 172.7, 199.9 ppm; MS (EI, 70 eV): m/z (%): 253.9 (100) [M^+]; Anal. Calcd for $C_9H_6N_2O_3S_2$: C, 42.51; H, 2.38; N, 11.02. Found: C, 40.82; H, 2.26; N, 10.45.

3-(2-Hydroxyethyl)-2-thioxo-1,3-thiazolidin-4-one (**21**): Pale yellow oil (17% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (t, J = 5.5 Hz, 2H), 4.01 (s, 2H), 4.25 (t, J = 5.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4, 46.6, 59.9, 174.6, 201.9 ppm; MS (EI, 70 eV): m/z (%): 177.0 (60) [M^+]; Anal. Calcd for $C_5H_7NO_2S_2$: C, 33.88; H, 3.98; N, 7.90. Found: C, 33.29; H, 4.12; N, 7.20.

Methyl 2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)hexanoate (**22**): Pale yellow oil (15% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.1 Hz, 3H), 1.10–1.38 (m, 4H), 2.13–2.29 (m, 2H), 3.72 (s, 3H), 3.98 (s, 2H), 5.51 (dd, J = 9.3, 5.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.3, 27.6, 28.2, 34.6, 52.7, 57.6, 168.7, 173.3, 201.0 ppm; MS (EI, 70 eV): m/z (%): 261.0 (55) [M^+]; Anal. Calcd for $C_{10}H_{15}NO_3S_2$: C, 45.95; H, 5.78; N, 5.36. Found: C, 47.24; H, 6.12; N, 5.84.

(4-Oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid (**23**): Pale yellow solid (<5% yield, not isolated). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (s, 2H), 4.77 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.6, 44.4, 171.0, 173.1, 200.2 ppm; MS (EI, 70 eV): m/z (%): 191.0 (94) [M^+].