A Convenient Synthesis of N-Substituted 2-Thioxo-1,3-thiazolidin-4-ones

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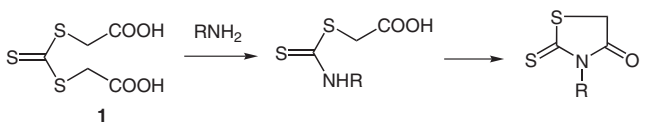
Abstract: A convenient method was developed for the synthesis of N-substituted rhodanines based on the reaction of amines, hydrazides, or acid thiohydrazides with trithiocarbonyl diglycolic acid in the presence of dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole.

Key words: oxamic acid thiohydrazides, amines, hydrazides, rhodanines, carbodiimide, 1,1′-carbonyldiimidazole

Rhodanines are widely used for the design of various compounds with useful properties.[1] The synthesis of antituberculosis agents based on 3-acylaminorhodanines has attracted considerable attention.[2,3] It was of interest to examine the possibility of preparing 3-thioacylaminorhodanines taking into account that a number of widely used antituberculosis drugs (for example, Protionamide-Akri, Ethionamide, and Thioacetazonum) contain the thioamide or thiohydrazide fragments.

Earlier, we have developed a convenient method for the preparation of oxamic acid thiohydrazides and used the latter for the synthesis of various heterocyclic compounds.[4,5] In continuation of these studies, we investigated the reaction of oxamic acid thiohydrazides with trithiocarbonyl diglycolic acid in expectation that 3-thioacylaminorhodanines will be produced by analogy with the known method.[6]

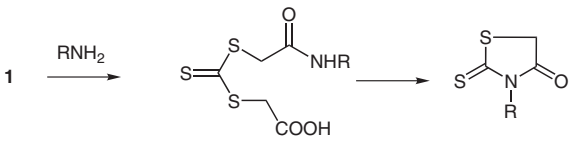
The advantage of the reactions involving trithiocarbonyl diglycolic acid is that they allow the one-pot synthesis of rhodanines starting from the corresponding amino-containing compounds. However, our attempts to prepare the target products according to a procedure developed for the synthesis of 3-acylaminorhodanines (in water in the presence of a base)[6] failed. It is assumed that the reaction involves the replacement of the thioglycolic fragment under the action of amine followed by cyclization to form the thiazolidine ring (Scheme 1).[7]



Scheme 1

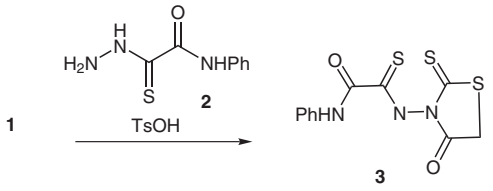
Conceivably, the bulky sulfur atom in oxamic acid thiohydrazides hinders the reaction with the carboxy group, whereas refluxing in basic aqueous media leads to decomposition of the starting thiohydrazide.

In our opinion, the process involving the reaction of amine with an activated carboxy group as the initial step and subsequent cyclization accompanied by the replacement of the thioglycolic group, which is a good leaving group (Scheme 2), could occur more smoothly. The carboxy group was activated with *p*-toluenesulfonic acid, dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole.



Scheme 2

We have studied the reaction of trithiocarbonyl diglycolic acid (**1**) with compound **2** in the presence of *p*-toluenesulfonic acid. Actually, it appeared that refluxing these reagents in toluene for six hours afforded rhodanine **3** in 49% yield (Scheme 3).



Scheme 3

It was found that substituted rhodanines are smoothly generated from oxamic acid thiohydrazides and trithiocarbonyl diglycolic acid with the use of a small excess of dicyclohexylcarbodiimide in THF at 0 °C. An increase in the reaction temperature led to a decrease in the yield of rhodanines. The order of addition of the reagents was demonstrated to have no effect on the yield of the product. However, in spite of rather high yields of rhodanines (70–80%), this method is not very convenient, because the products are difficult to separate from dicyclohexylurea that formed in the reaction.

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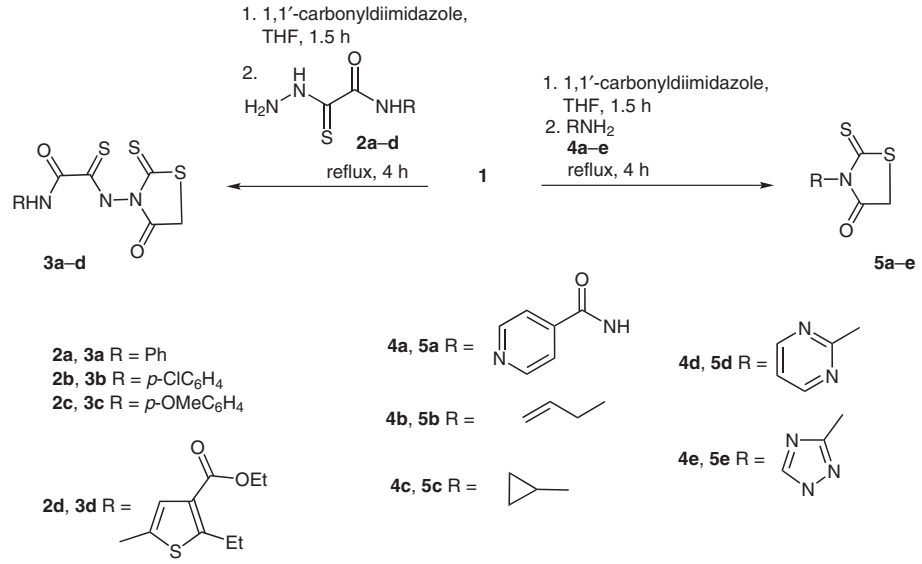

Scheme 4

A procedure for the synthesis of substituted rhodanines with the use of 1,1′-carbonyldiimidazole proved to be more convenient. The reaction was carried out in THF at room temperature. The addition of trithiocarbonyl diglycolic acid to 1,1′-carbonyldiimidazole and subsequent storage of the reaction mixture affords, apparently, an acylimidazole derivative, which smoothly reacts with oxamic acid thiohydrazides **2a–d** to give rhodanines **3a–d** in 75–88% yields (Scheme 4, Table 1). When the reagents were mixed simultaneously, resinification of the reaction mixture occurred. It was found that a twofold excess of 1,1′-carbonyldiimidazole should be used. When the latter compound was used in a smaller excess, the unconsumed starting thiohydrazide remained in the reaction mixture.

This is the general method for preparing various N-substituted rhodanines. This method does not require heating in basic aqueous media, which can lead to decomposition of the labile starting amines. The use of the modified approach made it possible to prepare the above-described rhodanines in substantially higher yields, as well as to synthesize compounds, which are impossible to prepare by the reaction with trithiocarbonyl diglycolic acid in water in the presence of a base.

For example, refluxing nicotinic acid hydrazides with trithiocarbonyl diglycolic acid in water in the presence of a base afforded nicotineaminorhodanine (**5a**) in 50% yield,[5] whereas the use of 1,1′-carbonyldiimidazole led to an increase in the yield of compound **5a** to 80–85% (Table 1). The reaction with aminocyclopropane **4c** in water produced rhodanine **5c** in 3% yield, whereas the reactions with allylamine (**4b**), 2-aminopyrimidine (**4d**), or 3-amino-1,2,4-triazole (**4e**) did not yield rhodanines at all. At the same time, the reactions performed in the presence of 1,1′-carbonyldiimidazole afforded the corresponding rhodanines **5b–e** in 80–85% yields (Table 1). The NMR data of compounds **3** and **5** prepared are listed in Table 2.

The proposed method allows one to prepare various N-substituted rhodanines in good yields from amino-containing compounds under mild conditions.

Table 1 Characteristic Data for Compounds **3a–d** and **5a–e**

Product	Yield (%)	Mp (°C)
3a	67	126–128
3b	73	183–184
3c	84	156–157
3d	77	167–168
5a	85	198–199 (Lit.[6] 197–198)
5b	82	43–45 (Lit.[8] 41–45)
5c	67	57–58 (Lit.[9] 54–55)
5d	92	141–142
5e	89	149–150

[a] Satisfactory microanalysis obtained:
C ± 0.18; H ± 0.22; N ± 0.19; S ± 0.17.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument in DMSO-d_6. The spin-spin coupling constants (J) are given in Hz. The mass spectra were obtained on a Kratos instrument using a direct inlet system; the ionization energy was 70 eV; the accelerating voltage was 1.75 kV. The melting points were measured on a Boetius hot-stage apparatus and are uncorrected. All reaction mixtures were analyzed and the purity of the products was checked by TLC (EtOAc–hexane, 1:1 as the eluent).

Oxamic acid thiohydrazides **2a–d** were synthesized as described earlier.[4,5] Trithiocarbonyl diglycolic acid (**1**) was prepared according to a known procedure.[10]

2-Thioxo-1,3-thiazolidin-4-ones 3a–d, 5a–e; General Procedure
A solution of trithiocarbonyl diglycolic acid (**1**; 0.12 g, 0.5 mmol) and 1,1′-carbonyldiimidazole (0.16 g, 1 mmol) in THF (10 mL) was

Table 2 Spectroscopic Data for **3a–d** and **5b–e**

Product	^{1}H NMR (300.13 MHz, DMSO-d_6) δ, *J* (Hz)	^{13}C NMR (75.47 MHz, DMSO-d_6) δ	MS *m*/*z* [M$^+$]
3a	4.2 (s, 2 H, SCH_2), 7.2 (t, *J* = 7.6, 1 H_{arom} *para* to N), 7.4 (t, *J* = 7.6, 2 H_{arom} *ortho* to N), 7.9 (d, *J* = 7.6, 2 H_{arom} *meta* to N), 10.7 (s, 1 H, NH)	37.387 (CH_2), 121.092 (CH_{arom} *ortho* to N), 125.037 (CH_{arom} *para* to N), 129.023 (CH_{arom} *meta* to N), 137.775 (C_{arom}), 169.015 (C=O), 193.623 (C=S)	312
3b	4.3 (s, 2 H, SCH_2), 7.5 (d, *J* = 8.7, 2 H_{arom} *ortho* to N), 7.9 (d, *J* = 8.7, 2 H_{arom} *meta* to N), 10.1 (s, 1 H, NH)	37.458 (CH_2), 122.654 (CH_{arom} *ortho* to N), 128.935 (CH_{arom} *meta* to N, *para* to N), 136.806 (C_{arom}), 169.015 (C=O), 193.623 (C=S)	346
3c	4.25 (s, 2 H, SCH_2), 7.0 (d, *J* = 8.9, 2 H_{arom} *ortho* to N), 7.65 (d, *J* = 8.9, 2 H_{arom} *meta* to N), 10.1 (s, 1 H, NH)	33.756 (CH_2), 53.687 (OCH_3), 116.963 (CH_{arom} *para* to N), 123.036 (CH_{arom} *ortho* to N), 131.852 (CH_{arom} *meta* to N), 137.21 (C_{arom}), 167.065 (C=O), 191.025 (C=S)	341
3d	1.25 (t, *J* = 7.44, 3 H, CH_3), 1.35 (t, *J* = 7.11, 3 H, CH_3), 2.7 (q, *J* = 4.77, 2 H, CH_2), 4.15 (s, 2 H, SCH_2), 4.35 (q, *J* = 4.08, 2 H, OCH_2), 7.0 (s, 1 H_{arom}), 11.8 (s, 1 H, NH)	14.201 (CH_3), 15.208 (CH_3), 22.042 (CH_2), 37.715 (CH_2 rhod), 60.524 (OCH_2), 114.101 (C_{thioph}), 119.935 (CH_{thioph}), 137.435 (C_{thioph}), 143.771 (C_{thioph}), 156.037 (C=O), 163.490 (C=O), 164.267 (C=S), 189.335 (C=S)	418
5b	3.7 (d, *J* = 7.44, 2 H, CH_2), 4.2 (s, 2 H, SCH_2), 5.2 (m, 2 H, $=CH_2$), 5.9 (m, 1 H, =CH)	38.248 (CH_2 rhod), 47.126 (CH_2N), 113.587 (CH_2=CH), 139.356 (CH_2=CH), 168.973 (C=O), 191.345 (C=S)	173
5c	1.2 (m, 4 H, CH_2CH_2), 1.7 (m, 1 H, NCH), 4.0 (s, 2 H, SCH_2)	12.478 (CH_2, cyclopropyl), 25.417 (CH, cyclopropyl), 38.410 (CH_2, rhod), 165.073 (C=O), 195.793 (C=S).	174
5d	4.25 (s, 2 H, SCH_2), 6.5 (d, *J* = 4.81, 1 H_{arom}), 6.6 (t, *J* = 4.77, 1 H_{arom}), 8.2 (d, *J* = 4.8, 1 H_{arom})	39.214 (CH_2), 110.207 (CH_{arom} *meta* to N), 157.959 (CH_{arom} *ortho* to N), 163.353 (C=S), 168.127 (C=O)	212
5e	4.25 (s, 2 H, SCH_2), 7.5 (s, 1 H, N=CH)	39.487 (CH_2), 145.344 (N=CH), 156.269 (C=O), 168.655 (C=S)	200

stirred at r.t. for 1.5 h. Then oxamic acid thiohydrazide **2a–d** (0.5 mmol) or the amine **4a–e** (0.5 mmol) was added, and the mixture was refluxed for 4 h. A 2 M HCl solution (30 mL) was added, and the mixture was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was recrystallized from MeCN (Tables 1 and 2).

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