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An Efficient One-Pot, Three-Component Synthesis of 5-Hydrazinoalkylidene Rhodanines from 1,2-Diaza-1,3-dienes

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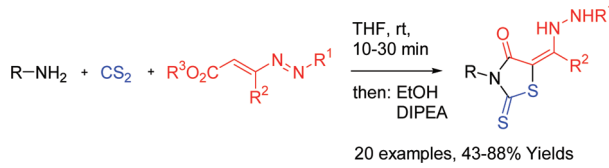
ABSTRACT



A novel three-component synthesis of 5-hydrazinoalkylidene rhodanine derivatives starting from aliphatic primary amines, carbon disulfide, and 1,2-diaza-1,3-dienes is described. The reaction proceeds successfully under both solution and solid-phase conditions.

Recently, multicomponent reactions (MCRs)[1] have received great attention from the chemical community because they permit the building of architecturally complex molecules from relatively simple starting materials. Although significant progress has been made in the area of MCRs, there is still a high demand for new processes aimed at the rapid assembly of heterocyclic molecules.

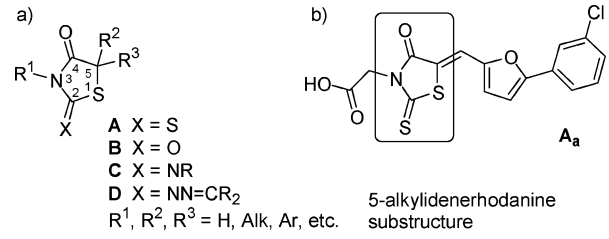


Figure 1. (a) Structures of 4-thiazolidinones. (b) Substituted 5-alkylidene rhodanines $\mathbf{A_a}$ as an important medicinal structure.

4-Thiazolidinones[2,3] are an important group of heterocyclic compounds, which have been subject to extensive study in the past years (Figure 1a). Among these 4-thiazolidinones, the rhodanine **A** (2-thioxothiazolidin-4-ones[4]) motif represents an important medicinal scaffold. Thus, 5-benzyliden-

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erhodanines have been reported as small molecule inhibitors of numerous targets such as cyclooxygenase and 5-lipoxygenase,[5a] β-lactamase,[5b] cathepsin D,[5c] HCV NS3 protease,[5d] aldose reductase,[5e] protein mannosyl transferase,[5f] protein tyrosine phosphatases,[5g] phosphodiesterase-4,[5h] and JNK-stimulating phosphatase.[5i]

Recent findings include the identification of certain substituted rhodanines (for example $\mathbf{A_a}$) as potential medicinal leads in developing therapeutic agents for the treatment of Alzheimer's disease[6] (Figure 1b). Furthermore, efficient synthetic inhibitors of anthrax lethal factor (ALF)[7] as well as small molecule matrix metalloprotease (MMP) inhibitors[8] containing novel rhodanine zinc-chelating groups have been identified.

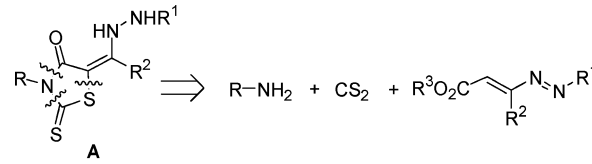
Standard procedures for the preparation of the 2-thioxothiazolidin-4-ones, including reactions of isothiocyanate with α-mercaptoacetic acid or its ester, reactions of ammonia or primary amines with carbon disulfide, and α-haloalkanoic acids are known.[2] While these protocols in general are suitable for construction of the rhodanine core, the 5-alkylidene rhodanine substructure may be accessed by coupling the thiazolidinone nucleus assembly with subsequent secondary transformations.[9] Despite the importance of these 5-unsaturated rhodanine derivatives, there are no reports that allow the direct formation of C5 hydrazinoalkylidene functionalized rhodanine from acyclic building blocks.

On the other hand, the utility of 1,2-diaza-1,3-dienes[10] in organic synthesis has been recognized for their ready accessibility and good reactivity from the high electrophilic (C4) center that can lead to a variety of heterocyclic rings by means of a wide range of nucleophiles.[10,11]

Moreover, it is well-known that amines with carbon disulfide and alkyl halides, epoxides, or Michael acceptors afford dithiocarbamates,[12] which have a variety of applications in organic, medicinal, material and agricultural chemistry. Recently, a simple and effective approach to the synthesis of rhodanine derivatives via three-component reactions in water has also been reported by Alizadeh et al.[13]

On the basis of these experiences, and in continuation of our ongoing interest in the discovery of new reactions for the synthesis of heterocycles from azo-ene systems, we designed a novel method for the preparation of 5-hydrazinoalkylidene rhodanines from amines, carbon disulfide, and 1,2-diaza-1,3-dienes (Scheme 1).

Scheme 1. Retrosynthetic Strategy for the Preparation of 5-Hydrazinoalkylidene Rhodanines



Initially,. we explored tentatively the reaction of benzylamine **1a** (1 mmol), carbon disulfide (1 mmol), and 1,2-diaza-1,3-diene **2a** (1 mmol) at room temperature in THF without the use of any base as catalyst. Under these conditions, we were delighted to obtain the product **4a** in 61% yield (Table 1, entry 1). In an attempt to improve the yield, we varied the molar ratios of the reagents. When a ratio of 1.5/1/3 was used, the reaction successfully gave the desired rhodanine **4a** in the best yield (83%) (Table 1, entry 3). The reaction was also carried out in different organic solvents such as EtOH, CH_2Cl_2, CH_3CN, H_2O, and DMF including solvent-free conditions (Table 1). In EtOH and CH_2Cl_2, the yields were similar to the ones in THF, while

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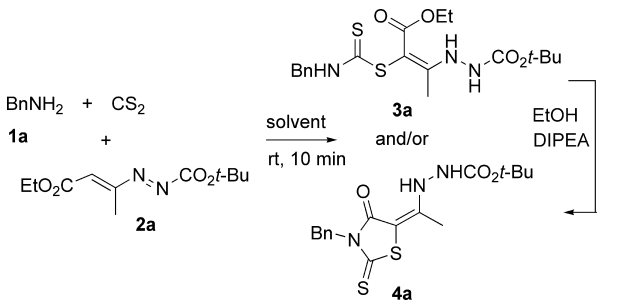
Table 1. Three-Component Reaction of Benzylamine **1a**, Carbon Disulfide, and 1,2-Diaza-1,3-diene **2a**: Optimization of the Reaction Conditions[a]



entry	solvent	molar ratios **1a/2a**/CS_2	product **3a** yield (%)	product **4a** yield (%)[c]
1	THF	1/1/1	—	63
2	THF	1/1/2	—	74
3	THF	1.5/1/3	—	83
4	Et_2O	1.5/1/3	77[b]	—
5	CH_3CN	1.5/1/3	72[b]	—
6	EtOH	1.5/1/3	—	81
7	neat	1.5/1/3	—	29
8	CH_2Cl_2	1.5/1/3	—	80
9	H_2O	1.5/1/3	—	trace
10	DMF	1.5/1/3	27	41

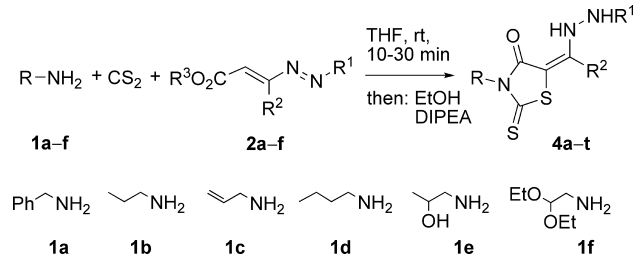
[a] All reactions were carried out in the appropriate solvent (10 mL) using benzylamine **1a**, CS_2, and 1,2-diaza-1,3-diene **2a** until complete disappearance of **2a** (at rt for 10 min, TLC check). [b] Yields of isolated product by precipitation. [c] Isolated yield after silica gel chromatography.

in the case of H_2O and neat condition the reaction proceeded with lower yields and formation of byproduct. Other solvents such as Et_2O and CH_3CN led exclusively to the formation of the adduct intermediate **3a** by simple precipitation from the crude reaction mixture. To obtain the relative rhodanine **4a** from compound **3a**, we carried out the heterocyclization process in EtOH and in the presence of DIPEA as base.

Having established the optimal conditions, we next examined the extension of these conditions and the efficiency of the protocol to other substrates by using several amines **1a**−**f** and different 1,2-diaza-1,3-dienes **2a**−**f**[14] (Table 2, entries 1−20). It is worth noting that the addition of DIPEA (1.0 mmol) at the disappearance of the 1,2-diaza-1,3-dienes **2a**−**f** (after 10−30 min, TLC check) is necessary to drive the process to completion by conversion of the dithiocarbamate acyclic intermediate **3** into final 5-hydrazinoalkylidene rhodanines **4a**−**f**.

In general, aliphatic primary amines such as benzylamine, *n*-propylamine, *n*-butylamine, allylamine, 1-amino-2-propanol, and 1-amino 2-acetaldehyde diethyl acetal worked well to give the corresponding heterocyclic compounds. Relatively hindered primary amines such as 1-phenylethylenamine and cyclohexylamine undergo efficient addition with 1,2-diaza-1,3-diene Michael acceptors to give the dithiocarbamate acyclic intermediate in excellent yields, but

Table 2. One-Pot Synthesis of 5-Hydrazinoalkylidene Rhodanines **4a**−**t**[a]



	amine **1**	1,2-diaza-1,3-diene **2**				product **4**	
entry	**1**	**2**	R^1	R^2	R^3	**4**	yield (%)[b]
1	**1a**	**2a**	CO_2t-Bu	Me	Et	**4a**	83
2	**1a**	**2b**	CO_2Me	Me	Et	**4b**	73
3	**1a**	**2c**	CO_2Bn	Me	Me	**4c**	56
4	**1a**	**2d**	CO_2Et	Me	Me	**4d**	83
5	**1a**	**2e**	CO_2Me	Et	Me	**4e**	85
6	**1a**	**2f**	C_6H_5	Me	Et	**4f**	43
7	**1b**	**2a**	CO_2t-Bu	Me	Et	**4g**	59
8	**1b**	**2b**	CO_2Me	Me	Et	**4h**	57
9	**1b**	**2c**	CO_2Bn	Me	Me	**4i**	52
10	**1b**	**2e**	CO_2Me	Et	Me	**4j**	73
11	**1c**	**2e**	CO_2Me	Et	Me	**4k**	44
12	**1c**	**2f**	C_6H_5	Me	Et	**4l**	69
13	**1d**	**2e**	CO_2Me	Et	Me	**4m**	59
14	**1d**	**2f**	C_6H_5	Me	Et	**4n**	82
15	**1d**	**2a**	CO_2t-Bu	Me	Et	**4o**	88
16	**1e**	**2b**	CO_2Me	Me	Et	**4p**	81
17	**1e**	**2c**	CO_2Bn	Me	Me	**4q**	54
18	**1f**	**2a**	CO_2t-Bu	Me	Et	**4r**	60
19	**1f**	**2b**	CO_2Me	Me	Et	**4s**	72
20	**1f**	**2d**	CO_2Et	Me	Me	**4t**	80

[a] Reaction conditions. For a detailed experimental operation, see Supporting Information. Amine (1.5 mmol), CS_2 (3.0 mmol), 1,2-diaza-1,3-diene (1.0 mmol), rt, 10 min (30 min when **2f** was used). [b] Isolated yield after silica gel chromatography.

only traces of the pertinent heterocycle were recovered. As expected, moreover, the aromatic amines did not participate in the reaction.

The structures of all products were established by spectroscopic methods.[15] The structure of **4i** was independently confirmed by X-ray crystal structure analysis (see Supporting Information). It is noteworthy that these rhodanine derivatives **4a**−**t** were obtained exclusively in the hydrazino isomer with *E* configuration.

On the basis of these findings and the well-established chemistry of dithiocarbamates, a plausible mechanism for the formation of hydrazinoalkylidene rhodanines **4** is presented in Scheme 2. Initially, the intermediate **3A** is produced by nucleophilic attack of the in situ generated dithiocarbamic acid **I** to the azo-ene system of 1,2-diaza-1,3-diene **2** via a Michael-like 1,4-addition reaction. Successively, hydrazono−hydrazino tautomerization of intermediates **3A** produces **3B** followed by base-promoted intramolecular nucleophilic attack of the NH dithiocarbamic group at the ester moiety with loss of the alcohol molecule and formation of compound **4** (Scheme 2).

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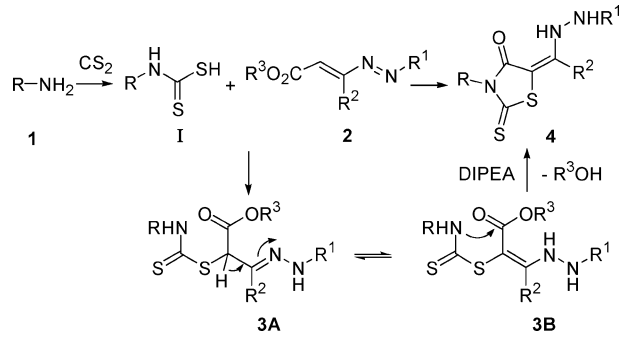
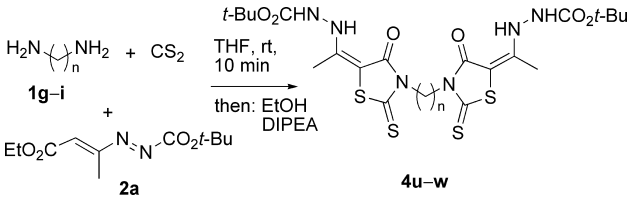
(14) 1,2-Diaza-1,3-dienes **1a**−**f** were synthesized from the corresponding chlorohydrazones by treatment with base (see Supporting Information).

Scheme 2. Plausible Mechanism for the Formation of 5-Hydrazinoalkylidene Rhodanine Derivatives **4**



To improve the usefulness of our synthetic protocol and with the aim to obtain molecules containing two differently spaced rhodanine rings, we next applied our procedure to the diamines **1g**−**i**. The use of ethylenediamine **1g**, 1,3-diaminopropane **1h**, and 1,4-diaminobutane **1i** gave rise to the di(5-hydrazinoalkylidene rhodanine) derivatives **4u**−**w** (Table 3).

Table 3. One-Pot Synthesis of Bis(5-hydrazinoalkylidene rhodanines) **4u**−**w**[a]

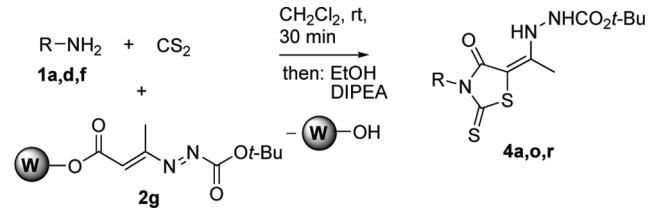


entry	amine **1**	*n*	product **4**	yield (%)[b]
1	**1g**	2	**4u**	64
2	**1h**	3	**4v**	59
3	**1i**	4	**4w**	65

[a] Reaction conditions. For a detailed experimental operation, see Supporting Information. Amine (0.75 mmol), CS_2 (3.0 mmol), 1,2-diaza-1,3-diene (1.0 mmol), rt, 10 min. [b] Isolated yield after silica gel chromatography.

In consideration of the mild and simple conditions required from these reactions in the liquid phase, we finally investigated the solid-phase[16] version of this methodology. Thus, Wang resin polymer-bound 1,2-diaza-1,3-diene **2g** (1.25 g) obtained by a modified procedure previously reported[17] readily reacted with 1.5 equiv of carbon disulfide and 0.75 equiv of amines **1a**,**d**,**f** in dichloromethane at room temperature to afford directly hydrazinoalkylidene rhodanines **4a**,**o**,**r** (Table 4). The overall

Table 4. Solid-Phase Synthesis of 5-Hydrazinoalkylidene Rhodanine Derivatives **4a**,**o**,**r**



entry	amine **1**	product **4**	yield (%)[b]
1	**1a**	**4a**	25
2	**1d**	**4o**	18
3	**1f**	**4r**	15

[a] Reaction conditions. For a detailed experimental operation, see Supporting Information. Amine (0.75 mmol), CS_2 (1.5 mmol), 1,2-diaza-1,3-diene (1.0 mmol), rt, 30 min. [b] Overall yields (after silica gel chromatography) for the multistep process of pure isolated **4a**,**o**,**r** with respect to the starting Wang resin.

yields for the multistep process of these solid-phase reactions are in the range of 15−25% and, therefore, comparable with the corresponding reactions in solution.

In summary, we have reported a novel, highly efficient, and selective three-component synthesis of 5-hydrazinoalkylidene rhodanine derivatives (exclusively in the *E*-hydrazino isomeric form) starting from aliphatic primary amines, carbon disulfide, and 1,2-diaza-1,3-dienes. When diamines were used in these reactions, di(5-hydrazinoalkylidene rhodanines) were also produced.

In addition, we have shown that this procedure can be applied successfully in a solid-phase approach. Therefore, the usefulness of the present MCR as a powerful method to obtain interesting final products, together with the mild and simple reaction conditions of these procedures (no dry solvents or inert atmosphere), makes it well suitable for the generation of combinatorial libraries.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. X-ray crystallographic data (CIF file) and ORTEP drawing of compound **4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For example, the hydrazinoalkylidene rhodanine **4a** has been elucidated as follows: (a) its IR spectrum exhibited strong absorption bands at 1707, 1658 (C=O), and 1191 cm^{-1} (C=S); (b) the ^1H NMR spectrum of **4a** in $CDCl_3$ showed two singlets attributed to the hydrazino (δ = 10.33 and 6.52 ppm) protons; (c) its ^{13}C NMR showed characteristic signals at δ = 191.2 (C=S), 166.7, 157.2 (C=O), 154.7, and 92.8 (C=C). (d) The mass spectrum of **4a** displayed a molecular ion peak at *m*/*z* = 379 [M^+].

(16) For a solid-phase synthesis of rhodanines by a different strategy, see: Lee, C. L.; Sim, M. M. *Tetrahedron Lett.* **2000**, *41*, 5729–5732.

(17) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Tietze, L. F. *Tetrahedron* **2001**, *57*, 5855–5863. For the modified procedure, see Supporting Information.