



Research Note

## A novel un-catalyzed and solvent-free method for the synthesis of 2-thioxothiazolidin-4-ones

S. Moghimi, M.M. Heravi\*, H.A. Oskooie and Y.S. Beheshtiha

Department of Chemistry, School of Science, Alzahra University, Tehran, P.O. Box 1993891176, Iran.

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### KEYWORDS

Rhodanine;  
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One-pot.

**Abstract.** An easy and highly efficient one-pot, three-component synthesis of rhodanines is reported. The reaction of primary amines, carbon disulfide and chloroacetyl chloride proceeded in the absence of solvent and catalyst, to afford 2-thioxothiazolidin-4-ones in good to excellent yields.

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### 1. Introduction

During the last few decades, Multi-Component Reactions (MCRs) have been studied as a facile route to assemble complex important structures in a small number of steps, while reducing production costs and environmental concerns. As a result, MCRs have attracted growing attention, leading to the development of new, highly selective methods for the synthesis of bioactive compounds such as natural products, drugs and agrochemicals [1].

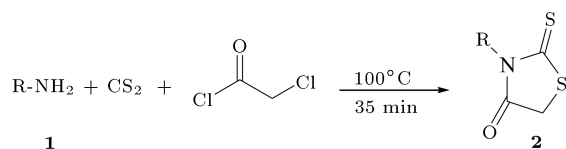
Rhodanines, an important 5-membered class of heterocyclic compounds, represent a privileged scaffold in drug discovery. Rhodanine based compounds and their analogues have an inherent tendency towards pharmacological and therapeutic activities, such as antibacterial, antifungal, antiviral, antimalarial, antitumor, anti-inflammatory and cardiogenic activities [2].

2-Thioxothiazolidin-4-ones are classically prepared [3] by the reaction of N-alkylthiocarbamate (formed in situ from an amine and carbon disul-

fide) with a  $\alpha$ -halocarbonyl compound [4,5], using acid [6], ammonium hydroxide [7] and triethylamine [8] as a catalyst. Recently, Chauhan reported a four-component, potassium carbonate catalyzed reaction, for the synthesis of ketene dithioacetal rhodanines, by the addition of alkyl halide to the mixture of amine,  $CS_2$  and ethyl chloroacetate [9].

Refluxing substituted anilines with bis (carboxymethyl)trithiocarbonate in water [10], the reactions of isothiocyanates with methyl thioglycolate in the presence of triethylamine [11], electrogenerated-base promoted electrosynthesis of carbamodithioates or cyclic rhodanines [12], are alternative methods to obtain the desired products. Alkylation of the rhodanine core also proceeds with  $Et_3N$  [13] and  $K_2CO_3$  [14]. These described methods have significant drawbacks, such as harsh reaction conditions, low yields, prolonged reaction times and the use of toxic solvents and catalysts. Therefore, the development of more facile and practical routes for the synthesis of rhodanines is still a highly desirable aim. As a part of our continuing research into the synthesis of heterocyclic compounds [15], in this paper, we wish to report a novel, efficient, solvent and catalyst free reaction for the synthesis of rhodanine derivatives.

\*. Corresponding author: Tel.: +98 21 88044051;  
Fax: +98 21 88041344  
E-mail address: mmh1331@yahoo.com (M.M. Heravi)



**Scheme 1.** The synthesis of thiazolidin-4-ones via a three-component reaction.

## 2. Results and discussion

The reaction of primary amines **1**, carbon disulfide and chloroacetyl chloride (Scheme 1) leads to the formation of 2-thioxothiazolidin-4-one derivatives **2** in excellent yields (Table 1). Without heating, the 1:1:1 adduct has been formed, but no cyclization occurred.

Elemental analysis, mass spectrometry, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, indicated beyond doubt the formation of *N*-substituted rhodanine derivatives. The mass spectrum of **2a** apparently displayed the expected molecular ion peak at  $m/z = 223$ , which confirmed that this derivative is a 1:1:1 adduct. The  $^1\text{H}$  NMR spectrum of **2a** in  $\text{CDCl}_3$ , contains two singlets at  $\delta = 3.9$  and  $\delta = 5.1$  ppm, along with multiplets for the aromatic protons. The  $^1\text{H}$  decoupled  $^{13}\text{C}$  NMR showed 8 distinct signals, with the resonance, due to  $\text{C}=\text{S}$ , appearing at  $\delta = 201.6$  ppm. A possible pathway is outlined in Scheme 2. The initial addition of amine to the carbon disulfide generates zwitterion **3** [16], which

is attacked by chloroacetyl chloride to produce **4**, loss of the  $\text{HCl}$  molecule and cyclization, which generates *N*-alkyl rhodanines **2** in 85–92% yield.

## 3. Conclusion

In summary, the un-catalyzed, solvent-free and one-pot method, for the synthesis of 2-thioxo-1,3-thiazolidin-4-ones is described. Mild reaction conditions, simplicity of procedure and short reaction time, make this route more convenient in comparison to previously reported protocols.

## 4. Experimental

All solvents and chemicals were used without further purification. Melting points were measured, using Bamstead Electrothermal 9200 apparatus.  $^1\text{H}$  and  $^{13}\text{C}$  NMR: Bruker DRX-500-Avance instrument; IR Spectra: FT-IR Bruker Tensor 27; EI-MS: Agilent-Technologies-(HP)-5937 mass spectrometer; Elemental analyses (C, H, N): Heraeus CHN-O-Rapid analyzer.

### 4.1. General procedure

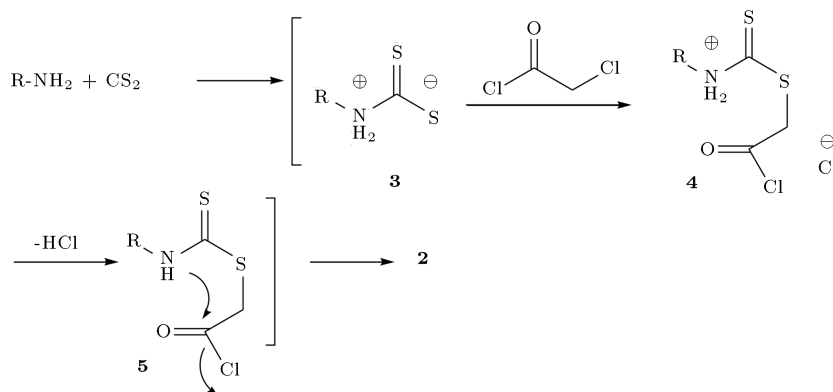
Chloroacetyl chloride (1 mmol) was added to a mixture of amine (1 mmol) and  $\text{CS}_2$  (5 mmol) at  $2^\circ\text{C}$ . The reaction mixture was allowed to warm up to room temperature and then was heated at  $100^\circ\text{C}$  for 35 minutes. After this time, the reaction mixture was washed with water, dried and subjected to short silica gel column chromatography ( $\text{SiO}_2$ : *n*-hexane/ $\text{AcOEt}$  4/1) to afford the pure title products as brown solids.

**3-Benzyl-2-thioxothiazolidin-4-one (2a):** Brown solid, yield: 0.19 g, (85%); M.p.:  $81^\circ\text{C}$  (Ref. [12]  $80$ – $81^\circ\text{C}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.96$  (2H, s,  $\text{CH}_2$ ), 5.18 (2H, s,  $\text{CH}_2$ ), 7.25–7.32 (3H, m, H-Ar), 7.41–7.44 (2H, dd,  $J = 7.7, 1.5$ , H-Ar) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 35.9$  ( $\text{CH}_2$ ), 47.9 ( $\text{CH}_2$ ), 129.6, 129.7, 132.2, 134.5 (4 CH-Ar), 174.4 ( $\text{C}=\text{O}$ ), 201.6 ( $\text{C}=\text{S}$ ) ppm; IR (KBr): 1733, 1675, 1451, 1335, 1268,

**Table 1.** Reaction of primary amines, carbon disulfide and chloroacetyl chloride.

Entry	R	Product	Yield <sup>a</sup> (%)
1	Bn	2a	85
2	4-Me-Bn	2b	88
3	4-OMe-Bn	2c	90
4	4-Cl-Bn	sd	87
5	Ph	2e	86
6	Me	2f	92
7	<i>c</i> -Hex	2g	90

<sup>a</sup>: Isolated yield



**Scheme 2.** The proposed mechanism for the formation of 2-thioxo-4-thiazolidin-4-ones.

1206, 1113, 757, 692  $\text{cm}^{-1}$ ; EI-MS:  $m/z$  (%) = 223 ( $\text{M}^+$ , 69), 148 (91), 104(15), 91 (100), 65 (46), 51 (17); Anal. Calcd (%) for  $\text{C}_{10}\text{H}_9\text{NOS}_2$ : C, 53.78; H, 4.06; N, 6.27. Found: C, 53.75; H, 4.1; N, 6.35.

3-(4-Methylbenzyl)-2-thioxothiazolidin-4-one (**2b**): Brown solid, yield: 0.21 g, (88%); M.p.: 69-71°C (Ref. [12] 71-72°C);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.32 (3H, s,  $\text{CH}_3$ ), 3.93 (2H, s,  $\text{CH}_2$ ), 5.13 (2H, s,  $\text{CH}_2$ ), 7.11 (2H-Ar, d,  $J$  = 7.87), 7.33 (2H-Ar, d,  $J$  = 7.9) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.62 ( $\text{CH}_3$ ), 35.84 ( $\text{CH}_2$ ), 47.82 ( $\text{CH}_2$ ), 129.54, 129.66, 132.19, 138.47 (4 CH-Ar), 174.31 ( $\text{C}=\text{O}$ ), 201.53 ( $\text{C}=\text{S}$ ) ppm; IR (KBr): 1724, 1666, 1422, 1339, 1307, 1216, 1184, 808  $\text{cm}^{-1}$ ; EI-MS:  $m/z$  (%) = 237 ( $\text{M}^+$ , 95), 162 (80), 146 (29), 105 (100), 91 (9), 77 (40), 65 (9), 51 (12); Anal. Calcd (%) for  $\text{C}_{11}\text{H}_{11}\text{NOS}_2$ : C, 55.67; H, 4.67; N, 5.90. Found: C, 55.70; H, 4.59; N, 5.96.

3-Phenyl-2-thioxothiazolidin-4-one (**2e**): Brown solid, yield: 0.18 g, (86%); M.p.: 183-185°C (Ref. [10c] 184-186°C);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.24 (2H, s,  $\text{CH}_2$ ), 7.22 ( $^1\text{H}$ -Ar, t,  $J$  = 7.4), 7.41 (2H-Ar, t,  $J$  = 7.8), 7.59 (2H-Ar, d,  $J$  = 7.7) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 36.8 ( $\text{CH}_2$ ), 118.9, 121.6, 132.2, 135.7 (4 CH-Ar), 174.5 ( $\text{C}=\text{O}$ ), 200.5 ( $\text{C}=\text{S}$ ) ppm; IR (KBr): 1730, 1643, 1494, 1343, 1218, 1186, 735, 700  $\text{cm}^{-1}$ ; EI-MS:  $m/z$  (%) = 209 ( $\text{M}^+$ , 73), 134 (100), 91 (25), 77 (35), 65 (19), 51 (55); Anal. Calcd (%) for  $\text{C}_9\text{H}_7\text{NOS}_2$ : C, 51.65; H, 3.37; N, 6.69. Found: C, 52.0; H, 3.21; N, 6.69.

3-Methyl-2-thioxothiazolidin-4-one (**2f**): Brown solid, yield: 0.136 g, (92%); M.p.: 72°C (Ref. [7] 71°C);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.36 (3H, s,  $\text{CH}_3$ ), 4.12 (2H, s,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 36.1 ( $\text{CH}_2$ ), 41.0 ( $\text{CH}_3$ ), 173.0 ( $\text{C}=\text{O}$ ), 201.3 ( $\text{C}=\text{S}$ ) ppm; IR (KBr): 1729, 1665, 1409, 1355, 1297, 1208, 1124, 791  $\text{cm}^{-1}$ ; EI-MS:  $m/z$  (%) = 147 ( $\text{M}^+$ , 97), 131 (18), 105 (26), 94 (24), 77 (39), 74 (89), 52 (100); Anal. Calcd (%) for  $\text{C}_4\text{H}_5\text{NOS}_2$ : C, 32.63; H, 3.42; N, 9.51. Found: C, 32.65; H, 3.64; N, 9.42.

3-Cyclohexyl-2-thioxothiazolidin-4-one (**2g**): Brown solid, yield: 0.194 g, (90%); M.p.: 116-118°C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.2-1.38 (3H, m), 1.62-1.68 (3H, m), 1.84-1.86 (2H, m), 2.26-2.33 (2H, m), 3.8 (2H, s,  $\text{CH}_2$ ), 4.82-4.88 (m,  $^1\text{H}$ ) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.64, 24.7, 25.6, 33.25, 33.49 (5  $\text{CH}_2$ ), 36.2 ( $\text{CH}_2$ ), 57.13 (CH), 175.6 ( $\text{C}=\text{O}$ ), 200.9 ( $\text{C}=\text{S}$ ) ppm; IR (KBr): 1743, 1677, 1455, 1345, 1258, 1201, 1143, 787  $\text{cm}^{-1}$ ; EI-MS:  $m/z$  (%) = 215 ( $\text{M}^+$ , 55), 134 (100), 81 (80), 67 (58), 55 (84), 51 (10); Anal. Calcd (%) for  $\text{C}_9\text{H}_{13}\text{NOS}_2$ : C, 50.2; H, 6.09; N, 6.50. Found: C, 49.81; H, 6.12; N, 6.41.

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## Biographies

**Setareh Moghimi** was born in Tehran, Iran, in 1984. She graduated in Chemistry in 2006 and received her MS degree in Organic Chemistry, in 2008, from Tehran University, Iran. She is currently pursuing her PhD degree in Organic Chemistry at Alzahra University, Tehran, Iran. Her research focuses on the application

of multi-component reactions in the synthesis of new heterocyclic compounds.

**Majid Momahed Heravi** was born in 1952 in Mashhad, Iran. He received his BSc degree from the National University of Iran in 1975 and his MSc and PhD degrees from Salford University England in 1977 and 1980. He completed his doctoral thesis under supervision of late Jim Clarck in Salford University, England. He started his career as a research fellow in Daroupakksh (a pharmaceutical company) in 1981 Tehran, Iran and joined as an assistant professor to Ferdowsi University of Mashhad. Iran in 1983 and promoted to associate professor in 1993 and full professor in 1997 in the aforementioned university. In 1999 he moved to Alzahra University Tehran, Iran as professor of chemistry where he is still working in. He has previously been a visiting professor at UC Riverside, California, USA and Hamburg University, Hamurg, Germany. His research interests focus on heterocyclic chemistry, catalysis, organic methodology and green synthetic organic chemistry.

**Hossein Abdi Oskooie** was born in 1943 in Oskoo, Iran. He got his final degree in organic chemistry in 1971 from university of Strasburg, France. He joined to department of chemistry in Tabriz University, Tabriz Iran as an assistant professor in 1972. He moved to department of chemistry in Alzahra University, Tehran Iran, in 1982. He promoted to associate professor and professor in Alzahra university. After 38 years working as a member of faculty he retired in 2011. He is still supervising MSc and PhD students at Alzahra University. His interest is heterocyclic chemistry and catalysis

**Seyed Yahya Shirazi Beheshtia** was born in Qazvin, Iran in 1951. He got his PhD degree in organic chemistry from Bradford University, UK in 1982. He joined department of Chemistry in Alzahra University, Tehran Iran as an assistant professor in 1986. He was promoted to associate professor in 1984 and still teaching and supervising MSc and PhD students at Alzahra University. His interest is heterocyclic chemistry and catalysis.