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Research Note

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

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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.

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 cardiotonic activities [2].

2-Thioxothiazolidin-4-ones are classically prepared [3] by the reaction of N-alkylthiocarbamate (formed in situ from an amine and carbon disulfide) with a α-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 (carboxylmethyl)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.

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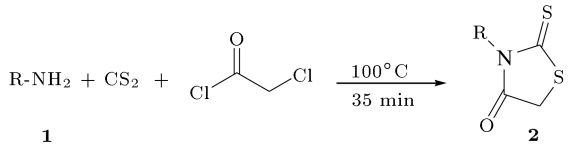


1 2

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}H and ^{13}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}H NMR spectrum of **2a** in $CDCl_3$, contains two singlets at $\delta = 3.9$ and $\delta = 5.1$ ppm, along with multiplets for the aromatic protons. The ^{1}H decoupled ^{13}C NMR showed 8 distinct signals, with the resonance, due to C=S, appearing at δ=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 HCl molecule and cyclization, which generates *N*-alkyl rhodanines **2** in 85-92% yield.

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

Entry	R	Product	Yield[a] (%)
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	*c*-Hex	2g	90

[a]: Isolated 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.

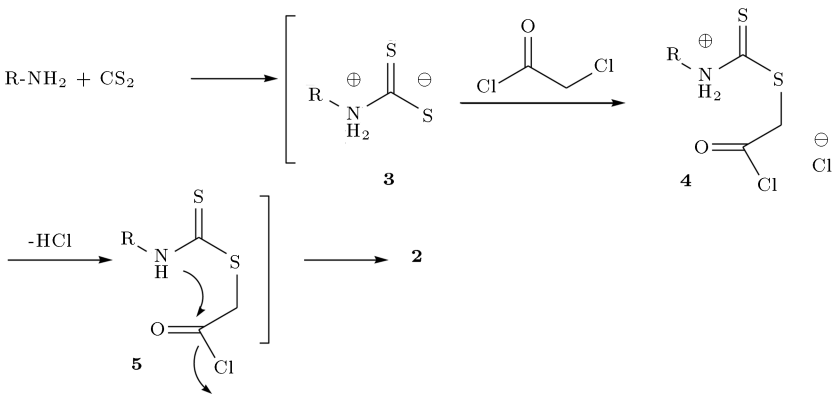
4. Experimental

All solvents and chemicals were used without further purification. Melting points were measured, using Bamstead Electrothermal 9200 apparatus. ^{1}H and ^{13}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 CS_2 (5 mmol) at 2°C. The reaction mixture was allowed to warm up to room temperature and then was heated at 100°C for 35 minutes. After this time, the reaction mixture was washed with water, dried and subjected to short silica gel column chromatography (SiO_2: *n*-hexane/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°C (Ref. [12] 80-81°C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.96$ (2H, s, CH_2), 5.18 (2H, s, 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}C NMR (125 MHz, $CDCl_3$): $\delta = 35.9$ (CH_2), 47.9 (CH_2), 129.6, 129.7, 132.2, 134.5 (4 CH-Ar), 174.4 (C=O), 201.6 (C=S) ppm; IR (KBr): 1733, 1675, 1451, 1335, 1268,



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

1206, 1113, 757, 692 cm^{-1}; EI-MS: m/z (%) = 223 (M^+, 69), 148 (91), 104(15), 91 (100), 65 (46), 51 (17); Anal. Calcd (%) for $C_{10}H_9NOS_2$: 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}H NMR (500 MHz, CDCl3): δ = 2.32 (3H, s, CH_3), 3.93 (2H, s, CH_2), 5.13 (2H, s, CH_2), 7.11 (2H-Ar, d, J = 7.87), 7.33 (2H-Ar, d, J = 7.9) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.62 (CH3), 35.84 (CH_2), 47.82 (CH_2), 129.54, 129.66, 132.19, 138.47 (4 CH-Ar), 174.31 (C=O), 201.53 (C=S) ppm; IR (KBr): 1724, 1666, 1422, 1339, 1307, 1216, 1184, 808 cm^{-1}; EI-MS: m/z (%) = 237 (M^+, 95), 162 (80), 146 (29), 105 (100), 91 (9), 77 (40), 65 (9), 51 (12); Anal. Calcd (%) for $C_{11}H_{11}NOS_2$: 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}H NMR (500 MHz, $CDCl_3$): δ = 4.24 (2H, s, CH_2), 7.22 (^{1}H-Ar, t, J = 7.4), 7.41 (2H-Ar, t, J = 7.8), 7.59 (2H-Ar, d, J = 7.7) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.8 (CH_2), 118.9, 121.6, 132.2, 135.7(4 CH-Ar), 174.5 (C=O), 200.5 (C=S) ppm; IR (KBr): 1730, 1643, 1494, 1343, 1218, 1186, 735, 700 cm^{-1}; EI-MS: m/z (%) = 209 (M^+, 73), 134 (100), 91 (25), 77 (35), 65 (19), 51 (55); Anal. Calcd (%) for $C_9H_7NOS_2$: 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}H NMR (500 MHz, CDCl3): δ = 3.36 (3H, s, CH_3), 4.12 (2H, s, CH_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.1 (CH_2), 41.0 (CH_3), 173.0 (C=O), 201.3 (C=S) ppm; IR (KBr): 1729, 1665, 1409, 1355, 1297, 1208, 1124, 791 cm^{-1}; EI-MS: m/z (%) = 147 (M^+, 97), 131 (18), 105 (26), 94 (24), 77 (39), 74 (89), 52 (100); Anal. Calcd (%) for $C_4H_5NOS_2$: 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}H NMR (500 MHz, $CDCl_3$): δ =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, CH_2), 4.82-4.88 (m, ^{1}H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ =24.64, 24.7, 25.6, 33.25, 33.49 (5 CH_2), 36.2 (CH_2), 57.13 (CH), 175.6 (C=O), 200.9 (C=S) ppm; IR (KBr): 1743, 1677, 1455, 1345, 1258, 1201, 1143, 787 cm^{-1}; EI-MS: m/z (%) = 215 (M^+, 55), 134 (100), 81 (80), 67 (58), 55 (84), 51 (10); Anal. Calcd (%) for $C_9H_{13}NOS2$: C, 50.2; H, 6.09; N, 6.50. Found: C, 49.81; H, 6.12; N, 6.41.

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