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A novel one-pot solvent-free synthesis of 3-alkyl-2-thioxo-1,3-thiazolidine-4-ones

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A novel one-pot solvent-free synthesis of 3-alkyl-2-thioxo-1,3-thiazolidine-4-ones

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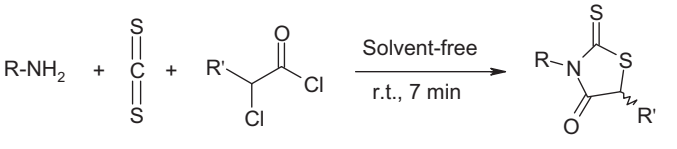
An easy, highly efficient solvent-free and simple one-pot approach to the synthesis of 3-alkyl-2-thioxo-1,3-thiazolidine-4-ones is reported. The reaction of a primary amine and carbon disulfide in the presence of chloroacetyl chloride or 2-chloro-2-phenylacetyl chloride at room temperature afforded 3-alkyl-2-thioxo-1,3-thiazolidine-4-one derivatives in high yields.



R: Alkyl,2-Methoxyethyl, substituted benzyl; R': H, Phenyl

Keywords: solvent-free reaction; rhodanines; primary amines; carbon disulfide

1. Introduction

During the last few decades, a central aim in synthetic organic chemistry has been to provide greener and more economically viable processes for the efficient synthesis of biologically active compounds with potential application in the pharmaceutical or agrochemical industries. One approach to this goal is to design reactions using solvent-free condition (*1*). It reduces the use of environmentally unsound organic solvents and diminishes the formation of other wastes. The reactions occur under mild conditions and usually need simple workup procedures using readily available equipment. Multicomponent reactions (MCRs) (*2*) are important to provide important routes for the synthesis of heterocyclic compounds. Although significant advances have been made in the case of MCRs, there is still a high demand for new processes for the synthesis of heterocyclic molecules. 4-Thiazolidinones are one of the most important groups of heterocyclic compounds (*3*). Among these 4-thiazolidinones, the rhodanine (2-thioxo-4-thiazolidinone) derivatives have been the subject of several studies in the past years. Rhodanine derivatives are used in analytical chemistry (*4*) as a sensitive reagent for the determination of ions. The application of rodanines as a

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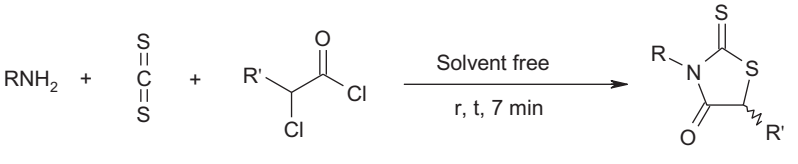
corrosion inhibitor of mild steel in acidic solution is well known (*5*). Rhodanine-based molecules have pharmacological activities that include anticancer (*6*), anticonvulsant (*7*), antibacterial, and antiviral activity (*8*). These compounds can also inhibit numerous targets such as bacterial MurD ligase (*9*), bacterial RNA polymerase (*10*), enoyl acyl carrier protein (ACP) reductase (*11*), histone acetyltransferases (*12*), ADAMTS-5 (*13*), and cholesterol esterase (*14*).

There are several reports about the synthesis of 2-thioxo-1,3-thiazolidine-4-one derivatives in the literature (*15*). However, most of the reported methods for the synthesis of these compounds require multiple-steps, toxic and harmful organic solvents, and also usually require a catalyst to facilitate the reaction. For example, one route for the synthesis of **5c** is reaction of *N*-isopropyldithiocarbamate with α-bromophenylacetic acid in the presence of a base, but this route is time-consuming and the yield of the reaction was only 30% (*15e*). Recently, a three-component reaction between primary amines and carbon disulfide in the presence of fumaryl chloride has been reported to produce 2-(3-alkyl-4-oxo-2-thioxo-1,3-thiazolidine-5-yl)acetic acid derivatives (*16*). Herein, we report an efficient one-pot solvent-free route for synthesis of 3-alkyl-2-thioxo-1,3-thiazolidine-4-one derivatives in high yields by the reaction of primary amines and carbon disulfide in the presence of chloroacetyl chloride or 2-chloro-2-phenylacetyl chloride.

2. Results and discussion

The reaction between primary amines and carbon disulfide in the presence of chloroacetyl chloride or 2-chloro-2-phenylacetyl chloride proceeds smoothly at room temperature and is completed within 7 min (Scheme 1).

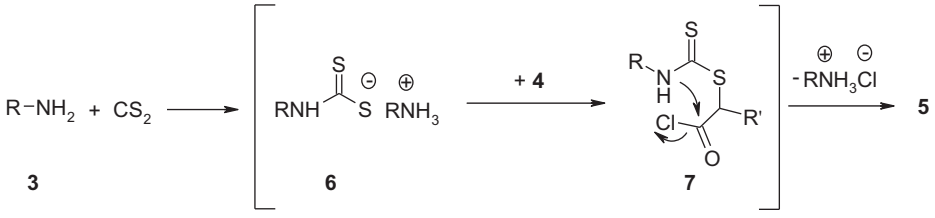
The structures of compounds **5c** and **5e** were deduced by the spectroscopic analysis and comparison of their physical data with those reported in the literature (*15b*, *15e*). The structures of other products were deduced from their IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic data. The mass spectrum of **5a** showed the molecular ion peak at $m/z = 267$. In the IR spectrum of **5a**, the C=O stretching absorption appeared at 1730 and the C=S group vibrated at 1324. The ^{1}H-NMR spectrum of **5a** showed two singlets at $\delta = 3.33$ and 5.26 ppm which were related to methoxy and



3 **4** **5 (80–87%)**

5	R	R'
5a	2-Methoxyethyl	Ph
5b	*i*-Pr	H
5c	*i*-Pr	Ph
5d	n-Bu	Ph
5e	Bn	Ph
5f	2-Chlorobenzyl	Ph
5g	2-Methoxybenzyl	Ph

Scheme 1. Solvent-free synthesis of 3-alkyl-2-thioxo-1,3-thiazolidine-4-one derivatives **5** (see Section 4).



Scheme 2. Proposed mechanism for the formation of 3-alkyl-2-thioxo-1,3-thiazolidine-4-one derivatives **5a**–**5g**.

methine protons and two multiplets at $\delta = 3.66$–3.70 and 4.26–4.30 for two methylene protons. Five aromatic protons appear as a multiplet at $\delta = 7.04$–7.37 ppm. The ^{13}C-NMR spectrum of **5a** showed 10 distinct signals in agreement with the proposed structure.

Although we have not established the mechanism of this reaction experimentally, a possible pathway is shown in Scheme 2. The reaction presumably proceeds through an initial addition of the amine **1** to carbon disulfide to afford alkylammonium dithiocarbamate salt **6** (*17*) which then reacts with 2-chloro-2-phenylacetyl chloride concomitant with the loss of alkylammonium chloride salt to produce the intermediate **7**, which undergoes intramolecular cyclization to generate compound **5** in high yield.

The reaction was also examined with aromatic amines under the same reaction conditions without success.

3. Conclusions

In conclusion, we have described a convenient solvent-free route for the synthesis of 3-alkyl-2-thioxo-1,3-thiazolidine-4-one derivatives of potential synthetic and pharmacological interest in high yield using simple and inexpensive starting materials. The simplicity and environmentally benign nature of the present procedure makes it an interesting route to produce functionalized rhodanine derivatives.

4. Experimental section

Melting points were measured with an Electrothermal 9100 apparatus. Elemental analyses C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-250 AVANCE instrument (300.1 and 250.1 MHz for ^{1}H and 75.5 and 62.9 MHz for ^{13}C) with $CDCl_3$ as solvent. Mass spectra were recorded with an Agilent-5975 C inert XL MSD mass spectrometer operating at an ionization potential of 70 eV. Amines, acetyl chlorides, and carbon disulfide were obtained from Merck and were used without further purification.

4.1. *General procedure for the preparation of 5a–5f (exemplified to 5a)*

To a magnetically stirred solution of 0.23 g 2-methoxyethylamine (3 mmol) was added 0.15 g CS_2 (2 mmol) at room temperature. The reaction mixture was then stirred for 2 min. Then, 0.19 g 2-chloro-2-phenylacetyl chloride (1 mmol) was added to the reaction mixture and the reaction mixture was allowed to stir for 5 min. After completion, the product was separated by column

chromatography over silica gel (Merck 230–400 mesh) using *n*-hexane-EtOAc mixture as eluent (8:1) to obtained product **5a**.

4.1.1. *3-(2-Methoxyethyl)-5-phenyl-2-thioxothiazolidine-4-one (**5a**)*

Yellow powder; yield 86%; m.p. 61–62°C. IR (KBr) (υ_{max}, cm^{-1}): 1730, 1324, 1118. ^{1}H-NMR (250.1 MHz, $CDCl_3$): δ 7.37–7.04 (m, 5H, Ar), 5.26 (s, H, CH-Ph), 4.30–4.26 (m, 2H, NCH_2), 3.70–3.66 (m, 2H, NCH_2CH_2), 3.33 (s, 3H, OMe). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 200.2 (C=S), 175.1 (C=O), 134.1 (C), 129.3 (2CH), 129.2 (CH), 128.3 (2CH), 68.0 (OCH_2), 58.8 (CH-Ph), 54.3 (OMe), 43.7 (NCH_2). MS (EI, 70 eV): m/z (%) = 267 (M^+, 7), 234 (24), 121 (50), 91 (100), 77 (20). Anal. Calcd for $C_{12}H_{13}NO_2S_2$ (267.04), C, 53.91; H, 4.90; N, 5.24; Found: C, 53.01; H, 4.85; N, 5.20%.

4.1.2. *3-Isopropyl-2-thioxo-1,3-thiazolidine-4-one (**5b**)*

Yellow oil; yield 82%. IR (KBr) (υ_{max}, cm^{-1}): 1730, 1314, 1253 cm^{-1}. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 5.24 (sept, 1H, $^3J_{HH}$ = 7.2 Hz, NCH), 3.84 (s, 2H, CH_2), 1.48 (d, 6H, $^3J_{HH}$ = 7.2 Hz, $2CH_3$).^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 202.1 (C=S), 174.2 (C=O), 50.4 (CH_2), 31.5 (NCH), 18.2 ($2CH_3$). MS (EI, 70 eV): m/z (%) = 175 (M^+, 65), 118 (100), 57 (35), 43 (58). Anal. Calcd for $C_6H_9NOS_2$ (175.26), C, 41.12; H, 5.18; N, 7.99; Found: C, 40.15; H, 5.09; N, 8.04%.

4.1.3. *3-Isopropyl-5-phenyl-2-thioxo-1,3-thiazolidine-4-one (**5c**)*

White powder; yield 80%; m.p. 123–125°C (15*e*). IR (KBr) (υ_{max}, cm^{-1}): 1733, 1318, 1100 cm^{-1}. ^{1}H-NMR (250.1 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, Ar), 5.28 (m, 1H, NCH), 5.07 (s, 1H, CH-Ph), 1.52–1.48 (m, 6H, $2CH_3$). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 200.1 (C=S), 175.2 (C=O), 134.1 (C), 129.4 (2CH), 129.1 (CH), 128.2 (2CH), 52.6 (CH-Ph), 50.5 (CH), 18.3 and 18.2 ($2CH_3$). MS (EI, 70 eV): m/z (%) = 251 (M^+, 99), 118 (100), 100 (74), 91 (48), 77 (15).

4.1.4. *3-Butyl-5-phenyl-2-thioxothiazolidine-4-one (**5d**)*

Pale yellow powder; yield 87%; m.p. 58–59°C. IR (KBr) (υ_{max}, cm^{-1}): 1735, 1325, 1189. ^{1}H-NMR (250.1 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H, Ar), 5.23 (CH-Ph), 4.03 (t, 2H, $^3J_{HH}$ = 7.5 Hz, NCH_2), 1.68–1.59 (m, 2H, CH_2), 1.43–1.26 (m, 2H, CH_2), 0.94 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_3). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 200.0 (C=S), 175.0 (C=O), 133.9 (C), 129.3 (2CH), 129.2 (CH), 128.2 (2CH), 54.3 (CH-Ph), 44.8 (NCH_2), 28.9 and 20.0 ($2CH_2$), 13.7 (CH_3). MS (EI, 70 eV): m/z (%)9 265 (M^+, 32), 232 (63), 118 (62), 105 (52), 91 (100), 77 (31). Anal. Calcd for $C_{13}H_{15}NOS_2$ (265.39), C, 58.83; H, 5.70; N, 5.28; Found: C, 58.50; H, 5.64; N, 5.11%.

4.1.5. *3-Benzyl-2-thioxo-1,3-thiazolidine-4-one (**5e**)*

White powder; yield 85%; m.p. 231–233°C (15*b*). IR (KBr) (υ_{max}, cm^{-1}): 1732, 1330, 1190 cm^{-1}. ^{1}H-NMR (250.1 MHz, $CDCl_3$): δ 7.53–7.11 (m, 10H, 2Ar), 5.47–5.16 (m, 3H, NCH_2, CH-Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 200.0 (C=S), 175.2 (C=O), 134.8 (C), 133.8 (C), 129.4 (2CH), 129.3 (CH), 128.9 (2CH), 128.7 (2CH), 128.4 (2CH), 128.3 (CH), 54.4 (CH-Ph), 47.9 (CH_2). MS (EI, 70 eV): m/z (%) = 299 (M^+, 56), 148 (41), 118 (73), 91 (100).

4.1.6. *3-(2-Chlorobenzyl)-5-phenyl-2-thioxothiazolidine-4-one (**5f**)*

White powder; yield 82%; m.p. 116–117°C. IR (KBr) (υ_{max}, cm^{-1}): 1726, 1329, 1191. ^{1}H-NMR (250.1 MHz, $CDCl_3$): δ 7.41–6.97 (m, 9H, 2Ar), 5.39–5.34 (m, 3H, NCH_2, CH-Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 199.4 (C=S), 174.6 (C=O), 133.4 (C), 133.0 (C), 131.7 (C), 129.8 (CH), 129.4 (2CH), 129.3 (CH), 128.9 (CH), 128.3 (2CH), 127.0 (CH), 126.9 (CH), 54.6 (CH-Ph), 45.6 (CH_2). MS (EI, 70 eV): m/z (%) = 298 (M–Cl, 100), 148 (14), 106 (28), 77 (15). Anal. Calcd for $C_{16}H_{12}ClNOS_2$ (333.00), C, 57.56; H, 3.62; N, 4.20; Found: C, 57.11; H, 3.70; N, 4.12%.

4.1.7. *3-(2-Methoxybenzyl)-5-phenyl-2-thioxothizaolidine-4-one (**5g**)*

White powder; yield 84%; m.p. 109–110°C. IR (KBr) (υ_{max}, cm^{-1}): 1731, 1336, 1199. ^{1}H-NMR (250.1 MHz, $CDCl_3$): δ 7.38–6.83 (m, 9H, 2Ar), 5.31–5.15 (m, 3H, NCH_2, CH-Ph), 3.74 (s, 3H, OMe). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 199.7 (C=S), 174.6 (C=O), 157.1 (C), 133.9 (C), 129.3 (2CH), 129.1 (CH), 128.9 (C), 128.3 (2CH), 128.0 (CH), 122.2 (CH), 120.2 (CH), 110.4 (CH), 55.3 (CH-Ph), 54.4 (OMe), 43.9 (CH_2). MS (EI, 70 eV): m/z (%) = 329 (M^+, 4), 136 (26), 121 (85), 91 (100), 77 (24). Anal. Calcd for $C_{17}H_{15}NO_2S_2$ (329.05), C, 61.98; H, 4.59; N, 4.25; Found: C, 62.56; H, 4.63; N, 4.32%.

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