A Novel Multicomponent Method for the Synthesis of 2-Thioxo-1,3-thiazolidin-4-ones

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Abstract: An easy, highly efficient and simple one-pot approach to the synthesis of 2-thioxo-1,3-thiazolidin-4-ones is reported. The reaction of a primary amine and carbon disulfide in the presence of fumaryl chloride in water afforded the title compounds in good yield.

Key words: thiazolidine, rhodanine, carbon disulfide, fumaryl chloride, multicomponent reaction

During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures,[1] with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry.[2] There are numerous biologically active molecules with five-membered rings containing two heteroatoms. Thiazolidine (**1**) and its derivatives are important scaffolds known to be important in several biologically active compounds.[3] Thiazolidine-2-thione (**2**) and thiazolidin-4-ones (**3**) are important substructures found in numerous natural products and pharmaceuticals (Figure 1).[4]

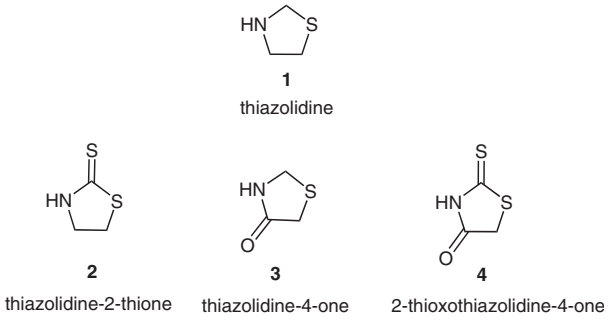

Figure 1

Compounds containing the 2-thioxothiazolidin-4-one ring **4** (rhodanine) and its derivatives have shown a wide range of pharmacological activities, which include antimicrobial,[5] antiviral,[6] and anticonvulsant[7] activity. Additionally, rhodanine-based molecules have been popular as small molecule inhibitors of numerous targets such as HCV NS3 protease,[8] aldose reductase,[9] β-lactamase,[10] and histidine decarboxylase,[11] and have been used as antidiabetic agents.[12] For example, **5** is an antagonist against anti-apoptotic Bcl-2 proteins,[13] and **6** was evaluated as an inhibitor of translation initiation (Figure 2).[14]

As part of our ongoing project devoted to the synthesis of heterocycles, especially those containing two heteroatoms,[15] we report herein a novel, one-pot, three-component synthesis of 2-thioxothiazolidin-4-one in water.

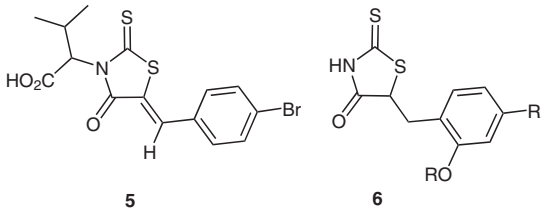

Figure 2

Recently, we have become interested in the application of fumarylchloride in multicomponent reactions.[16] Thus, as shown in Scheme 1, we investigated its reaction with zwitterions derived from primary amines **7** and carbon disulfide in water.[17] The reaction, which is complete after 12 hours at room temperature, produces the 2-(3-alkyl-4-oxo-2-thioxo-1,3-thiazolan-5-yl)acetic acid derivatives **8** in 75–85% yields (Table 1).

The structures of 2-(3-alkyl-4-oxo-2-thioxo-1,3-thiazolan-5-yl)acetic acid derivatives were elucidated from their elemental analysis, mass, IR and highfield ^{1}H and ^{13}C NMR spectra as described for **8a**. The mass spectrum of **8a** displayed the molecular ion peak (*m*/*z* = 281) and, importantly, an ion peak (*m*/*z* = 237) indicating CO_2 loss and thus the presence of a CO_2H group. In the IR spectrum, the O–H stretching absorption band of the acid appeared between 3451–2625 cm^{-1}, with peaks at 1718 and 1671 cm^{-1} due to the two carbonyl groups, and absorptions at 1343 and 1186 cm^{-1} indicating the presence of a C=S moiety.

The ^{13}H NMR spectrum of **8a**, contains three double doublets at δ = 3.04 (*J* = 18.0, 9.0 Hz), 3.60 (*J* = 18.0, 3.5 Hz) and 4.45 ppm (*J* = 8.9, 3.5 Hz), which are related to the diastereotopic hydrogens of C*H*$_2$CO$_2$H and the SC*H*, respectively. The spectrum also contains two doublets at δ = 5.15 and 5.24 ppm (*J* = 14.2 Hz) arising from the two diastereotopic hydrogens of C*H*$_2$Ph, and the acidic hydrogen, which appears as a broad signal between δ = 6.50 and 8.00 ppm. The ^{1}H decoupled ^{13}C NMR spectrum showed ten distinct signals, in agreement with the proposed struc-

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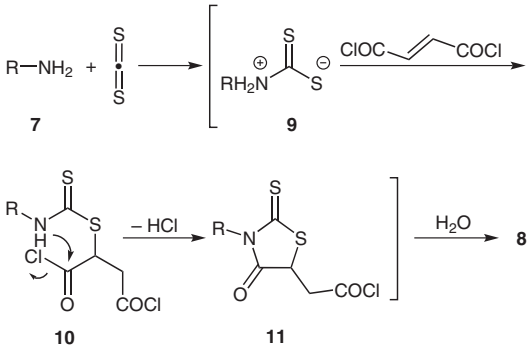
ture, with the resonance due to C=S, appearing at δ = 200.05 ppm.

Although we have not established the mechanism experimentally, a possible pathway is proposed in Scheme 1. The reaction presumably proceeds through initial addition of amine **7** to the carbon disulfide to afford zwitterion **9**,[17] which then attacks the conjugated double bond to produce intermediate **10**.[18] Probably, the thiocarbamate **10** undergoes intramolecular cyclization followed by loss of an HCl molecule to convert it into the thiazolidine **11** (it is important to note that five-membered-ring formation is kinetically more favorable than six-membered-ring formation).[19] Finally, hydrolysis of intermediate **11** leads to the corresponding 2-thioxo-1,3-thiazolidin-4-ones **8** in 75–85% yield.[20]



Scheme 1 Proposed mechanism for the formation of 2-thioxo-1,3-thiazolidin-4-one derivatives

In summary, in this communication we report a novel and concise method for the synthesis of 2-thioxo-1,3-thiazolidin-4-ones of potential synthetic and pharmacological interest in good yields using simple and inexpensive starting materials. The one-pot reaction is performed under neutral conditions and the carboxylic acid group on the 5-position is capable of further functionalization. The simplicity of the present procedure makes it an interesting alternative to more complex multistep approaches.

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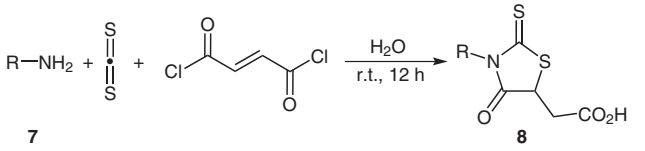
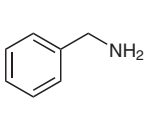
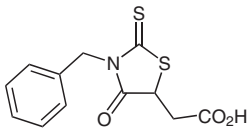
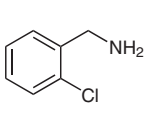
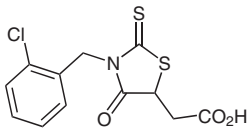
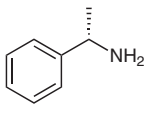
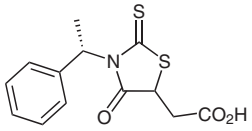
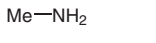
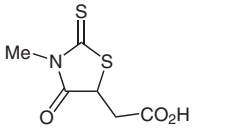
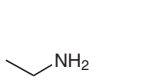
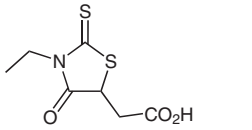
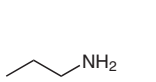
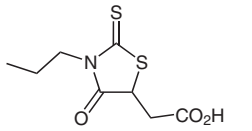
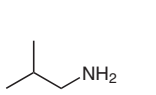
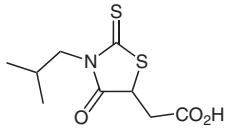
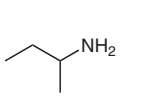
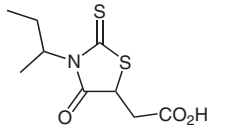
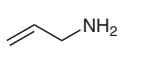
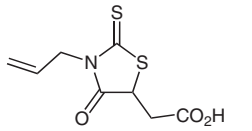
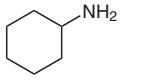
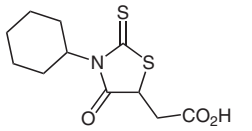
Table 1 The Reaction of Primary Amine **7**, Carbon Disulfide, and Fumaryl Chloride at Room Temperature



Entry	Primary amine **7**	Product **8**	Yield (%)
a			85
b			82
c			80
d			75
e			87
f			80
g			75
h			77
i			75
j			78

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(20) To a magnetically stirred mixture of benzylamine (0.11 g, 1 mmol) and H_2O (3 mL as solvent), was added CS_2 (0.15 g, 2 mmol). Then, fumaryl chloride (0.15 g, 1 mmol) was added and the reaction mixture was allowed to stir for 12 h. The reaction was extracted with CH_2Cl_2 (2 × 8 mL), and the solvent was dried and evaporated. The residue was purified by column chromatography (*n*-hexane–EtOAc, 4:1) to obtain product **8a** as a yellow wax (0.24 g, 85%). IR (KBr): 3451–2625 (OH), 1718 (CO_2H), 1671 (CO), 1343 and 1186 (C=S) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.04 (1 H, dd, $^2J_{H,H}$ = 18.0 Hz, $^3J_{H,H}$ = 9.0 Hz, CHCH_2), 3.60 (1 H, dd, $^2J_{H,H}$ = 18.0 Hz, $^3J_{H,H}$ = 3.5 Hz, CHCH_2), 4.45 (1 H, dd, $^3J_{H,H}$ = 8.9 Hz, $^3J_{H,H}$ = 3.5 Hz, CHCH$_2$), 5.15 (1 H, d, $^3J_{H,H}$ = 14.2 Hz, CH_2Ph), 5.24 (1 H, d, $^3J_{H,H}$ = 14.2 Hz, CH_2Ph), 7.30 (2 H, t, $^3J_{H,H}$ = 7.2 Hz, 2 × CH of Ph), 6.51–7.37 (1 H, br, OH), 7.40 (1 H, t, $^3J_{H,H}$ = 7.7 Hz, CH of Ph), 7.45 (2 H, d, $^3J_{H,H}$ = 7.1 Hz, 2 × CH of Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 36.33 (CHCH$_2$), 45.46 (CHCH$_2$), 47.83 (CH$_2$Ph), 128.16 (CH of Ph), 128.59 (2 × CH of Ph), 128.86 (2 × CH of Ph), 134.60 (C_{ipso}-CH$_2$), 174.06 (NCO), 175.39 (CO_2H), 200.05 (C=S). MS: *m*/*z* (%) = 281 (58) [M^+], 265 (11), 237 (17), 148 (68), 91 (100), 77 (9), 65 (27), 55 (10). Anal. Calcd for $C_{12}H_{11}NO_3S_2$ (281.34): C, 51.23; H, 3.94; N, 4.98. Found: C, 51.29; H, 3.97; N, 4.95. Compound **8f**: Yield: 0.19 g (80%). Yellow wax. IR (KBr): 3350–2610 (OH), 1719 (CO_2H), 1679 (CO), 1348 and 1125 (C=S) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 0.94 (3 H, t, $^3J_{H,H}$ = 7.4 Hz, NCH$_2$CH$_2$CH_3), 1.63–1.70 (2 H, m, NCH$_2$CH_2CH$_3$), 3.02 (1 H, dd, $^2J_{H,H}$ = 18.2 Hz, $^3J_{H,H}$ = 9.2 Hz, CHCH_2), 3.28 (1 H, dd, $^2J_{H,H}$ = 18.0 Hz, $^3J_{H,H}$ = 3.4 Hz, CHCH_2), 3.95 (2 H, t, $^3J_{H,H}$ = 7.5 Hz, NCH_2CH$_2$CH$_3$), 4.42 (1 H, dd, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,H}$ = 3.6 Hz, CHCH$_2$), 6.01–7.21 (1 H, br, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 11.14 (NCH$_2$CH$_2$$CH_3$), 20.08 (NCH$_2$$CH_2CH_3$), 36.63 (CH$CH_2$), 45.54 ($CHCH_2$), 46.33 (N$CH_2CH_2CH_3$), 173.91 (NCO), 175.59 (CO_2H), 200.57 (C=S). MS: *m*/*z* (%) = 233 (100) [M^+], 215 (18), 200(10), 187 (31), 174 (22), 146 (15), 100 (61), 86 (32), 43 (30). Anal. Calcd for $C_8H_{11}NO_3S_2$ (233.30): C, 41.19; H, 4.75; N, 6.00. Found: C, 41.23; H, 4.77; N, 6.05. Compound **8i**: Yield: 0.17 g (75%). Yellow wax. IR (KBr): 3445–3060 (OH), 1717 (CO_2H), 1677 (CO), 1333 and 1200 (C=S) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.04 (1 H, dd, $^2J_{H,H}$ = 17.6 Hz, $^3J_{H,H}$ = 8.7 Hz, CHCH_2), 3.29 (1 H, dd, $^2J_{H,H}$ = 17.6 Hz, $^3J_{H,H}$ = 3.5 Hz, CHCH_2), 4.45 (1 H, dd, $^3J_{H,H}$ = 8.6 Hz, $^3J_{H,H}$ = 3.4 Hz, CHCH$_2$), 4.60–4.63 (2 H, m, CH_2N), 5.23–5.30 (2 H, m, CH=CH_2), 5.77–5.80 (1 H, m, CH=CH$_2$), 6.35–7.28 (1 H, br, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 36.50 (CHCH$_2$), 45.59 (CHCH$_2$), 46.65 (NCH$_2$), 119.58 (CH=CH$_2$), 129.33 (CH=CH$_2$), 173.93 (NCO), 175.10 (CO_2H), 199.88 (C=S). MS: *m*/*z* (%) = 231 (39) [M^+], 216 (44), 197 (27), 187 (51), 149 (45), 98 (57), 86 (39), 71 (61), 58 (78), 55 (100), 42 (73). Anal. Calcd for $C_8H_9NO_3S_2$ (231.28): C, 41.55; H, 3.92; N, 6.06. Found: C, 41.56; H, 3.95; N, 6.07.