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An efficient method for the transformation of 5-ylidenerhodanines into 2,3,5-trisubstituted-4-thiazolidinones

Danylo Kaminskyy [a], Dmytro Khyluk [a], Olexandr Vasylenko [b], Roman Lesyk [a,*]

[a] Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska 69, Lviv 79010, Ukraine
[b] Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Science of Ukraine, Murmanska 1, Kyiv 02094, Ukraine

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ABSTRACT

The use of 3-substituted-2-mercaptoacrylic acids, synthesized via hydrolysis of 5-ylidenerhodanines for the preparation of 2,3,5-trisubstituted-4-thiazolidinones via a new variant of the one-pot, three-component reaction has been studied.

4-Thiazolidinones belong to privileged scaffolds in modern medicinal chemistry and their derivatives possess a wide spectrum of biological activity.[1–3] 2,3-Disubstituted-4-thiazolidinone derivatives are the most investigated and they function as antiviral,[4,5] anti-inflammatory,[6] antimicrobial,[7,8] antiasthmatic,[9] and antiproliferative[10,11] agents. The most convenient method for 2-substituted-4-thiazolidinone synthesis is the one-pot, three-component reaction of a primary amine, an oxo-compound, and a thiolic agent using various reaction conditions, such as extended heating with a dehydrating agent, using an acylation agent, or microwave-assisted organic synthesis.[8,12–16] Taking into consideration the critical influence of the presence and the nature of the C5 fragment on the biological activity, introduction of the aforementioned substituent is one of the most effective methods for 4-thiazolidinone structural modification.[1,17] This approach can be realized using different mercapto-derivatives such as 2-mercaptopropionic and 3-mercaptosuccinic acids and others in cyclocondensation reactions. However, the presence of an ylidene moiety at the C5 position is desirable for biological activity, especially anticancer activity.[1,3,17] The synthesis of 5-ylidene-4-thiazolidinones via Knoevenagel reaction, commonly using acetic acid and sodium acetate as the catalysts is not effective due to the low reactivity of the methylene group of 2-substituted-4-thiazolidinone in comparison with rhodanine (2-thioxo-4-thiazolidinone) or 2,4-thiazolidinedione derivatives.[18]

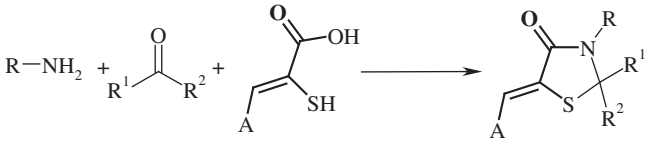
Hence, the aim of the present Letter was the synthesis of 5-ylidene-2,3-disubstituted-4-thiazolidinones via a novel one-pot, three-component reaction.

The possibility of using 3-substituted-2-mercaptoacrylic acids as thiolic agents in a one-pot, three-component reaction was proposed based on the retrosynthetic approach for 5-ylidene-2,3-disubstituted-4-thiazolidinones shown in Scheme 1.

For the synthesis of 3-substituted-2-mercaptoacrylic acids we used alkaline hydrolysis of accessible 5-ylidenerhodanines **1**[19] (Scheme 2), to obtain the appropriate thiolic agents **2**.[20] The 5-ylidene-2,3-disubstituted-4-thiazolidinones **3a–g** were successfully obtained using a one-pot, three-component reaction based on primary amines, aldehydes or cyclohexanone and thiolic agents **2** (Method a).[21]

The target compounds **3a–g** were also synthesised using Method b from 5-unsubstituted-2,3-substituted-4-thiazolidinones **4** via Knoevenagel reaction.[21] The yields of target compounds **3a–g** using Method b were in the range 35–56%.[22]

The structures of the synthesized compounds were elucidated from spectral data.[22] The ^{1}H NMR spectra of 2-arylsubstituted-4-



Scheme 1. General scheme for the synthesis of 2,3,5-trisubstituted-4-thiazolidinones.

* Corresponding author. Tel./fax: +38 032 275 7734.
E-mail address: dr_r_lesyk@org.lviv.net (R. Lesyk).

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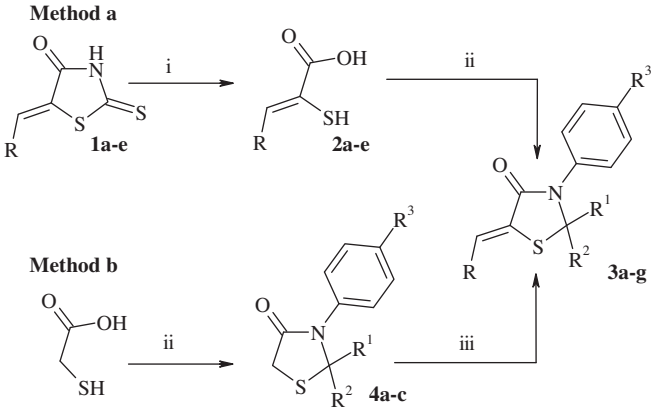

3	R	R^1; R^2 or R^1+R^2	R^3
a	4-Cl-C_6H_4	H; Ph	Me
b	4-Cl-C_6H_4	H; 4-Me_2N-C_6H_4	Cl
c	4-MeO-C_6H_4	H; Ph	Me
d	4-MeO-C_6H_4	$(CH_2)_5$	Cl
e	4-Me_2N-C_6H_4	H; Ph	Me
f	Ph-CH=CH	H; Ph	Me
g	2-HO-C_6H_4	$(CH_2)_5$	Cl

Scheme 2. Synthesis of 5-ylidene-2,3-disubstituted-4-thiazolidinones **3**. Reagents, conditions and yields: (i) **1** (1.0 equiv), NaOH (5.0 equiv) 30% aq solution, reflux, 0.5 h; conc. HCl (5.0 equiv) solution, 89–95%; (ii) **2** or thioglycolic acid (1.0 equiv), appropriate amine (0.5 equiv), appropriate aldehyde or cyclohexanone (0.5 equiv), benzene, reflux, 24 h, 56–78% (compounds **3**), 60–71% (compounds **4**); (iii) **4** (1.0 equiv), appropriate aldehyde (1.1 equiv), KO*t*-Bu (1.5 equiv), *i*-PrOH, reflux, 3 h, 57–78%.

thiazolidinones **3a–c,e,f** showed a singlet at ~4.70–6.85 ppm due to a CH group. The chemical shift of the methylidene group of the 5-arylidene derivatives was in the range 7.40–8.00 ppm. Signals at ~6.0 ppm representative of *E*-isomers were not observed. This indicated formation of *Z*-isomers, as in the case of rhodanine or 2,4-thiazolidinone derivatives.[1,23,24] The signals of the aromatic protons and cyclohexyl fragment were at expected values.

Newly synthesized compounds **3a–c, 3e** and **3g** were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program (http://www.dtp.nci.nih.gov) for in vitro cell line screening to investigate their anticancer activity. Anticancer assays were performed according to the US NCI protocol.[25–27] The tested compounds (concentration 10^{-5} M) showed insignificant anticancer activity—having weak average values (based on 60 cancer cell lines) of anticancer activity, however, they possessed specific influence on some cancer cell lines.[28] The leukemia panel was the most sensitive to the tested compounds

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20. Preparation of 3-substituted-2-mercaptoacrylic acids **2**. A 30% aq solution of NaOH (50 mmol) was added to 5-ylidenerhodanine **1** (10 mmol). The reaction mixture was refluxed for 30 min and cooled. An equimolar amount of conc. HCl was added and the mixture was diluted with H_2O (150 ml). The product was filtered and recrystallized from EtOH or EtOH/H_2O (1:1).
21. Preparation of 5-ylidene-2,3-disubstituted-4-thiazolidinones **3**. *Method a*: A mixture of appropriate amine (5 mmol), aldehyde or cyclohexanone (5 mmol) and 3-substituted-2-mercaptoacrylic acid **2** (10 mmol) in benzene was refluxed for 24 h using a Dean–Stark apparatus. The reaction mixture was added to an aq solution of $NaHCO_3$, after cooling. The crude precipitate was filtered and recrystallized from AcOH. *Method b*: Preparation of 2,3-substituted-4-thiazolidinones **4**. A mixture of the appropriate amine (8 mmol), aldehyde or cyclohexanone (8 mmol) and thioglycolic acid (16 mmol) in benzene was refluxed for 24 h using a Dean–Stark apparatus. After cooling, the mixture was added to an aq solution of $NaHCO_3$. The crude precipitate was filtered and recrystallized from AcOH or EtOH. Preparation of 5-ylidene-2,3-disubstituted-4-thiazolidinones **3**. A mixture of appropriate 2,3-disubstituted-4-thiazolidinone **4** (5 mmol), aromatic aldehyde (5.5 mmol), KO*t*-Bu (7.5 mmol) and *i*-PrOH (15 ml) was refluxed for 3 h. AcOH (1 ml) was added after cooling. The product was filtered and recrystallized from AcOH.
22. Spectral and analytical data for compounds **3**. 5-(4-Chlorobenzylidene)-2-phenyl-3-(4-methyphenyl)-4-thiazolidinone (**3a**). Yield 78% (Method a), 53% (Method b), mp >230 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 2.24 (s, 3H, CH_3), 6.79 (s, 1H, 2-H), 7.10 (d, J = 8.2 Hz, 2H, Ar), 7.22–7.31 (m, 5H, Ar), 7.35 (d, J = 7.35 Hz, 2H, Ar), 7.45 (d, J = 8.5 Hz, 2H, Ar), 7.49 (s, 1H, CH=), 7.55 (d, J = 8.5 Hz, 2H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): 165.0, 138.9, 136.8, 135.2, 134.1, 133.3, 131.3, 129.8, 129.5, 129.4, 127.6, 127.5, 126.0, 123.6, 63.0, 21.0. Anal. Calcd for $C_{23}H_{18}ClNOS$,% C, 70.49; H, 4.63; N, 3.57. Found,%: C, 70.60; H, 4.75; N, 3.90.
5-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-2-(4-dimethylaminophenyl)-4-thiazolidinone (**3b**). Yield 56% (Method a), 35% (Method b), mp >230 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 2.88 (s, 6H, 2 × CH_3), 6.54 (d, J = 8.8 Hz, 2H, Ar), 6.72 (s, 1H, 2-H), 7.15 (d, J = 8.8 Hz, 2H, Ar), 7.31 (d, J = 8.8 Hz, 2H, Ar), 7.41–7.45 (m, 4H, Ar), 7.47 (s, 1H, CH=), 7.54 (d, J = 8.8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): 164.8, 139.3, 135.4, 133.7, 133.5, 133.3, 131.3, 130.1, 129.4, 129.2, 127.4, 128.5, 128.2, 125.8, 115.0, 62.8, 45.0. Anal. Calcd for $C_{24}H_{20}Cl_2N_2OS$. C, 63.30; H, 4.43; N, 6.15. Found,%: C, 63.50; H, 4.55; N, 6.40.
5-(4-Methoxybenzylidene)-2-phenyl-3-(4-methyphenyl)-4-thiazolidinone (**3c**). Yield 71% (Method a), 47% (Method b), mp >230 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 2.21 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.84 (s, 1H, 2-H), 7.04 (d, J = 8.3 Hz, 2H, Ar), 7.13 (d, J = 7.9 Hz, 2H, Ar), 7.22–7.37 (m, 7H, Ar), 7.51 (s, 1H, CH=), 7.52 (d, J = 8.8 Hz, 2H, Ar), ^{13}C NMR (100 MHz, DMSO-d_6): 165.5, 159.86, 139.3, 136.6, 135.4, 131.4, 129.8, 129.4, 129.3, 127.8, 127.4, 126.0, 125.0. 123.6, 115.0, 62.7, 55.8, 21.0. Anal. Calcd for $C_{24}H_{21}NO_2S$. C, 74.39; H, 5.46, N, 3.61. Found,%: C, 74.55; H, 5.65; N, 3.80.
4-(4-Chlorophenyl)-2-(4-methoxybenzylidene)-1-thia-4-aza-spiro[4.5]decan-3-one (**3d**). Yield 71% (Method a), 48% (Method b), mp 194–197 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 0.93–1.00 (m, 1H, cyclohex.), 1.49–1.60 (m, 3H, cyclohex.), 1.68 (m, 2H, cyclohex.), 1.77 (m, 2H, cyclohex.), 2.00 (m, 2H, cyclohex.), 3.80 (s, 3H, OCH_3), 7.07 (d, J = 8.4 Hz, 2H, Ar), 7.34 (d, J = 8.2 Hz, 2H,

Ar), 7.37 (s, 1H, CH=), 7.58 (d, J = 8.2 Hz, 4H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): 166.2, 159.9, 135.8, 134.0, 133.1, 131.3, 129.8, 127.9, 124.6, 122.9, 114.9, 73.7, 55.8, 39.3, 24.1, 24.0. Anal. Calcd for $C_{22}H_{22}ClNO_2S$. C, 66.07; H, 5.54; N, 3.50. Found,%: C, 66.20; H, 5.70; N, 3.60.

5-(4-Dimethylaminobenzylidene)-2-phenyl-3-(4-methyphenyl)-4-thiazolidinone (**3e**). Yield 73% (Method a), 56% (Method b), mp >230 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 2.24 (s, 3H, CH_3), 2.97 (s, 6H, $N(CH_3)_2$), 6.67 (s, 1H, 2-H), 6.77 (d, J = 7.6 Hz, 2H, Ar), 7.11 (d, J = 7.4 Hz, 2H, Ar), 7.22–7.42 (m, 9H, Ar), 7.45 (s, 1H, CH=). ^{13}C NMR (100 MHz, DMSO-d_6): 164.6, 139.4, 139.3, 136.3, 135.3, 131.3, 129.3, 129.1, 127.9, 127.7, 127.5, 124.5, 123.6, 122.2, 114.7, 62.6, 41.2, 20.9. Anal. Calcd for $C_{25}H_{24}N_2OS$. C, 74.97; H, 6.04; N, 6.99. Found,%: C, 75.10; H, 6.20; N, 7.15.

2-Phenyl-5-(3-phenylallylidene)-3-(4-methyphenyl)-4-thiazolidinone (**3f**). Yield 75% (Method a), 42% (Method b), mp >230 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 2.20 (s, 3H, CH_3), 6.81 (s, 1H, 2-H), 6.84–6.91 (m, 1H, Ar), 6.97–7.00 (m, 1H, Ar), 7.03–7.14 (m, 3H, Ar), 7.16–7.22 (m, 1H, Ar), 7.23–7.42 (m, 9H, Ar), 7.55 (d, J = 7.9 Hz, 2H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6): 173.8, 164.8, 139.4, 138.3, 136.8, 136.6, 135.4, 129.8, 129.4, 129.3, 129.1, 128.9, 127.5, 127.4, 125.8, 124.9, 124.6, 62.7, 21.0. Anal. Calcd for $C_{25}H_{21}NOS$. C, 78.30; H, 5.52; N, 3.65. Found,%: C, 78.50; H, 5.65; N, 3.80.

4-(4-Chlorophenyl)-2-(2-hydroxybenzylidene)-1-thia-4-aza-spiro[4.5]decan-3-one (**3g**). Yield 75% (Method a), 42% (Method b), mp >230 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 0.90–1.06 (m, 1H, cyclohex.), 1.49–1.73 (m, 7H, cyclohex.), 1.93–2.03 (m, 2H, cyclohex.), 6.89–6.96 (m, 2H, Ar), 7.14–7.23 (m, 1H, Ar), 7.32 (d, J = 8.6 Hz, 2H, Ar), 7.47–7.53 (m, 1H, Ar), 7.56 (d, J = 8.6 Hz, 2H, Ar), 7.70 (s, 1H, CH=), 10.07 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): 164.3, 151.2, 135.3, 134.1, 133.2, 130.1, 129.1, 127.5, 127.3, 124.1, 123.5, 118.2, 113.3, 75.1, 39.2, 23.9, 24.0. Anal. Calcd for $C_{21}H_{20}ClNO_2S$. C, 65.36; H, 5.22; N, 3.63. Found,%: C, 65.50; H, 5.30; N, 3.70.

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28. Compounds **3a–c**, **3e**, and **3g** were evaluated toward a panel of 60 human tumor cell lines at a concentration of 10^{-5} M and showed the following mean growth percent values: **3a**—90.54%, **3b**—109.56%, **3c**—97.11%, **3e**—98.75% and **3g**—85.82%. However, growth percent values decreased for selected leukemia cell lines under the action of compounds **3a**, **3c** and **3g**: *K562*—27.25%, *RPMI-8226*—39.76%, *SR*—62.30% (compound **3a**); *HL-60(TB)*—61.22%, *RPMI-8226*—64.84%, *SR*—60.47% (compound **3c**); *MOLT-4*—65.22%, *RPMI-8226*—67.76% (compound **3g**).