Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

A convenient solvent-free and one-pot synthesis of 4-hydroxythiazolidine-2-thiones

Farough Nasiri[a], Amin Zolali[b] & Mohammad Ahmadiazar[b]
[a] Department of Applied Chemistry, Faculty of Science, University of Mohaghegh Ardabili, P.O. Box 56199-11367, Ardabil, Iran
[b] Department of Chemistry, Faculty of Science, University of Kurdistan, Sanandaj, Iran
Published online: 15 Apr 2014.

To cite this article: Farough Nasiri, Amin Zolali & Mohammad Ahmadiazar (2014): A convenient solvent-free and one-pot synthesis of 4-hydroxythiazolidine-2-thiones, Journal of Sulfur Chemistry, DOI: 10.1080/17415993.2014.907407

To link to this article: http://dx.doi.org/10.1080/17415993.2014.907407

Journal of Sulfur Chemistry, 2014
http://dx.doi.org/10.1080/17415993.2014.907407

Taylor & Francis
Taylor & Francis Group

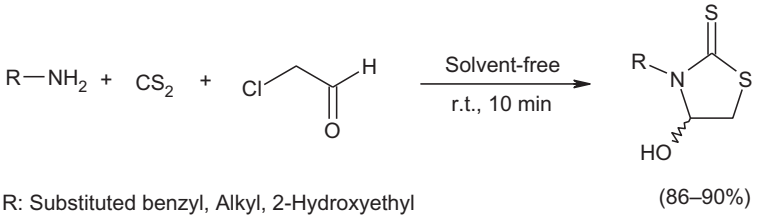
A convenient solvent-free and one-pot synthesis of 4-hydroxythiazolidine-2-thiones

Farough Nasiri[a]*, Amin Zolali[b] and Mohammad Ahmadiazar[b]

[a]*Department of Applied Chemistry, Faculty of Science, University of Mohaghegh Ardabili, P.O. Box 56199–11367, Ardabil, Iran;* [b]*Department of Chemistry, Faculty of Science, University of Kurdistan, Sanandaj, Iran*

(*Received 24 July 2013; accepted 19 March 2014*)

A highly efficient solvent-free and simple one-pot approach for the synthesis of 4-hydroxythiazolidine-2-thione is described. The reaction of primary amines and carbon disulfide in the presence of 2-chloroacetaldehyde afforded the title compounds in high yields.



R: Substituted benzyl, Alkyl, 2-Hydroxyethyl

(86–90%)

Keywords: 2-chloroacetaldehyde; primary amines; dithiocarbamate; carbon disulfide

1. Introduction

In recent years, carrying out reactions under solvent-free conditions has been developed. These reactions occur under mild conditions which minimizes the generation of waste as well as the use of dangerous organic solvents.[1,2] Due to the presence of sulfur atoms in many biologically and pharmaceutically active molecules (for a list of the top selling sulfur-containing drugs in 2012 with structures, see: http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.) its introduction into organic compounds has received much attention in organic synthesis.[3–7]

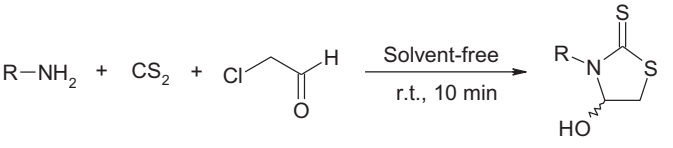
Organic dithiocarbamates, found in a variety of biologically active molecules,[8,9] are important compounds that have numerous biological and medicinal characteristics.[10–12] These compounds are also of interest in industry, for example, they are used as vulcanization accelerators in the rubber industry.[13] There are several reports about the synthesis of 4-hydroxythiazolidine-2-thione derivatives with α-haloketones in the literature.[14–18] The reactions between amines and amino acids with carbon disulfide in the presence of 2-chloroacetaldehyde have been also reported.[19,20] However, these reactions occur in the presence of a base and usually require long

*Corresponding author. Email: nasiri@uma.ac.ir

reaction times. As a consequence, the 4-hydroxythiazolidine-2-thiones formed in these reactions are not isolated and instead often undergo dehydration in high yields. Herein, we report an efficient and convenient solvent-free synthesis of 4-hydroxythiazolidine-2-thione derivatives from the reaction of primary amines and carbon disulfide in the presence of 2-chloroacetaldehyde.

2. Results and discussion

The solvent-free reaction between primary amines **1** and carbon disulfide in the presence of 2-chloroacetaldehyde **2** affords 4-hydroxythiazolidine-2-thione derivatives **3** in high yields (Scheme 1).



1 **2** **3a–3f**

3	R	Yield%
a	Benzyl	87
b	2-Chlorobenzyl	89
c	Ethyl	90
d	2-Hydroxyethyl	88
e	Phenethyl	88
f	Propyl	86

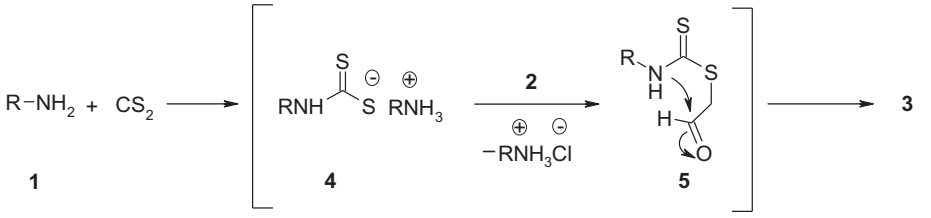
Scheme 1. Synthesis of 4-hydroxythiazolidine-2-thione derivatives **3a**–**3f** (see Section 4).

The structures of **3a**–**3f** *were* deduced from their elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and mass spectrometric data. The ^{1}H NMR spectrum of **3a** ($CDCl_3$) exhibited a multiplet at 7.38–7.35 ppm identified as phenyl group. The methylene protons of benzyl group appeared as an AX system ($\delta_A = 5.66$ and $\delta_X = 4.52$ ppm, $J_{AX} = 14.7$ Hz). The methine proton in **3a** appeared as a broad doublet ($\delta = 5.49$ ppm, $J = 5.8$ Hz) and the methylene protons of the thiazolidine ring showed an AMX system ($\delta_A = 3.57$ and $\delta_M = 3.16$ ppm, $J_{AM} = 12.4$ Hz, $J_{AX} = 6.5$ Hz, and $J_{MX} = 1.7$ Hz). The OH group appeared as a broad peak at $\delta = 3.37$ ppm. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed eight distinct signals in agreement with the proposed structure. The mass spectrum of **3a** showed the molecular ion peak at the appropriate m/z value.

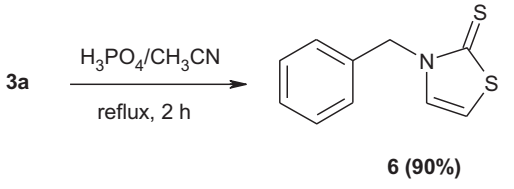
Although the mechanism of the above reaction is unknown, a possible mechanism for this reaction is proposed in Scheme 2. The reaction starts by the addition of amine to carbon disulfide to form alkylammonium dithiocarbamate salt **4**,[21–23] which subsequently attacks the 2-chloroacetaldehyde to produce acyclic dithiocarbamate **5**. This intermediate undergoes intramolecular cyclization to generate compound **3** in high yield.

To provide additional confirmation of structure **3**, the product **3a** was dehydrated with a catalytic amount of H_3PO_4 in MeCN (Scheme 3).

In the ^{1}H NMR spectrum of **6** the OH peak was absent and the olefinic protons resonated as two doublets at $\delta = 6.94$ and $\delta = 6.57$ ppm with a coupling constant of 6.0 Hz. The ^{13}C NMR spectrum of **6** also verifies the removal of the OH group and the newly formed olefinic carbons appeared at $\delta = 111.1$ and $\delta = 130.8$ ppm (see Experimental section). We also examined the



Scheme 2. Proposed mechanism for the formation of compound **3**.



Scheme 3. Dehydration reaction of compound **3a**.

acetylation reaction of compound **3a** using acetic anhydride at room temperature. In this case, the dehydrated product **6** was the only product obtained. This result shows that acetic anhydride dehydrate compounds **3** under very mild conditions even in comparison to H_3PO_4.

3. Conclusion

In conclusion, we have reported a convenient solvent-free route for the synthesis of 4-hydroxythiazolidine-2-thione derivatives of potential synthetic interest in good yields using simple and inexpensive starting materials. The 4-hydroxythiazolidine-2-thione derivatives can be easily converted to the related dehydrated compounds. The simplicity and environmentally friendly nature of the present procedure makes it an interesting method to produce functionalised dithiocarbamates.

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 MHz for ^{1}H and 75.5 MHz for ^{13}C) with $CDCl_3$ or DMSO-d_6 as solvent. Mass spectra were recorded with an Agilent-5975 C inert XL MSD mass spectrometer operating at an ionisation potential of 70 eV. Amines, 2-chloroacetaldehyde, and carbon disulfide were obtained from Merck and used without further purification.

4.1. *General procedure for the preparation of 4-hydroxythiazolidine-2-thione derivatives (3a–f)*

To a magnetically stirred mixture of primary amine (2 mmol) and CS_2 (2 mmol) was added 2-chloroacetaldehyde (2 mmol, 45% in water) and the reaction mixture was allowed to stir for 10 min. After completion, the reaction mixture was purified by column chromatography over

silica gel (Merck 230–400 mesh) using the *n*-hexane–EtOAc mixture as eluent (5:1) to obtain product **3**.

4.1.1. *3-Benzyl-4-hydroxythiazolidine-2-thione (**3a**)*

White powder; yield 87%; mp 104 − 105°C. IR (KBr) (υ_{max}, cm^{-1}): 3325, 1462, 1306, 1238, 1163. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.38–7.35 (m, 5H, Ar), 5.09 (AX system, $\delta_A = 5.66$ and $\delta_X = 4.52$ ppm, $J_{AX} = 14.7$ Hz, 2H, NCH_2), 5.48 (bd, 1H, $J = 5.8$ Hz, CH), 3.57 and 3.16 (AMX system, $\delta_A = 3.57$ and $\delta_M = 3.16$ ppm, $J_{AM} = 12.4$ Hz, $J_{AX} = 6.4$ Hz and $J_{MX} = 1.8$ Hz, 2H, SCH_2), 3.37 (bs, 1H, OH).^{13}C NMR (75.5 MHz, $CDCl_3$): δ 197.1 (C9S), 135.2 (C), 129.0 and 128.4 (4CH), 128.3 (C), 88.4 (OCH), 49.5 (NCH_2), 36.1 (CH_2). EI-MS (m/z): 225 (M^+, 25), 207 (50), 148 (38), 91 (100). Anal. Calcd for $C_{10}H_{11}NOS_2$ (225.32): C, 53.31; H, 4.92; N, 6.22; Found: C, 52.67%; H, 4.89%; N, 6.10%.

4.1.2. *3-(2-Chlorobenzyl)-4-hydroxy thiazolidine-2-thione (**3b**)*

White powder; yield 89%; mp 149 − 150°C. IR (KBr) (υ_{max}, cm^{-1}): 3241, 1471, 1299, 1236, 1174. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.46–7.40 and 7.30–7.27 (2m, 5H, CH-Ph, CH), 5.20 (AX system, $\delta_A = 5.61$ and $\delta_B = 4.79$ ppm, $J_{AX} = 15.3$ Hz, 2H, NCH_2), 3.63 and 3.18 (AMX system, $\delta_A = 3.63$ and $\delta_M = 3.18$ ppm, $J_{AM} = 12.4$ Hz, $J_{AX} = 6.3$ Hz, and $J_{MX} = 1.5$ Hz, 2H, SCH_2), 3.33 (bd, 1H, $J = 9.5$ Hz, OH).^{13}C NMR (75.5 MHz, $CDCl_3$): δ 191.2 (C9 S), 133.7 and 132.9 (2C), 130.3, 129.8, 129.6, and 127.4 (4CH), 88.6 (CHOH), 47.1 (NCH_2), 36.1 (CH_2). EI-MS (m/z): 260 (M^+, 5), 224 (100), 206 (60), 125 (80), 89 (50). Anal. Calcd for $C_{10}H_{10}ClNOS_2$ (259.77): C, 46.24; H, 3.88; N, 5.39; Found: C, 46.10%; H, 3.80%; N, 5.29%.

4.1.3. *3-Ethyl-4-hydroxythiazolidine-2-thione (**3c**)*

Brown oil; yield 90%. IR (KBr) (υ_{max}, cm^{-1}): 3380, 1474, 1363, 1264, 1117. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 5.69 (m, 1H, CH),4.20 (bs, 1H, OH), 4.07 and 3.66 (2m, 2H, NCH_2), 3.60 and 3.18 (2m, 2H, SCH_2), 1.26 (t, $^3J_{HH} = 7.2$ Hz, 3H, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$): δ 196.1 (C9 S), 89.3 (CHOH), 42.0 (NCH_2), 36.3 (SCH_2), 12.5 (CH_3). EI-MS (m/z): 163 (M^+, 90), 145 (32), 116 (44), 90 (100). Anal.Calcd for $C_5H_9NOS_2$ (163.25): C, 36.79; H, 5.56; N, 8.58; Found: C, 36.70%; H, 5.60%; N, 8.62%.

4.1.4. *4-Hydroxy-3-(2-hydroxyethyl) thiazolidine-2-thione (**3d**)*

Brown oil; yield: 88%.IR (KBr) (υ_{max}, cm^{-1}): 3353, 1465, 1306, 1232, 1173. ^{1}H NMR (300.1 MHz, DMSO-d^6): δ 4.97 (bs, 1H, OH), 3.95 (m, 1H, CH), 3.68–3.21 (m, 7H, $3CH_2$, OH).^{13}C NMR (75.5 MHz, DMSO-d^6): δ 195.3 (C9 S), 90.0 (CHOH), 57.7 (OCH_2), 48.3 (NCH_2), 35.3 (SCH_2). EI-MS (m/z):179 (M^+, 25), 161 (100), 117 (98), 77 (30), 58 (70). Anal.Calcd for $C_5H_9NO_2S_2$ (179.25): C, 33.50%; H, 5.06%; N, 7.81%; Found: C, 33.48%; H, 5.00%; N, 7.75%.

4.1.5. *4-Hydroxy-3-phenethylthiazolidine-2-thione (**3e**)*

White powder; yield 88%; mp 116 − 117°C. IR (KBr) (υ_{max}, cm^{-1}):3315, 1464, 1310, 1222, 1148. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H, CH-Ph), 5.17 (m, 1H, CH), 4.30 and 3.83–3.72 (2m, 3H, NCH_2, OH), 3.45 and 3.05 (AMX system, $\delta_A = 3.45$ and $\delta_M = 3.05$ ppm, $J_{AM} = 12.3$ Hz, $J_{AX} = 6.5$ Hz, and $J_{MX} = 2.0$ Hz, 2H, SCH_2), 3.10–2.99 (m, 2H, CH_2Ph).^{13}C

NMR (75.5 MHz, CDCl3): δ 196.4 (C9 S), 138.3 (C), 128.8 and 128.7 (4CH), 126.9 (CH), 90.4 (CHOH), 48.6 (NCH_2), 36.3 (SCH_2), 33.2 (CH_2Ph). EI-MS (m/z): 239 (M^+, 60), 117 (50), 104 (100), 91 (67), 77 (63). Anal.Calcd for $C_{11}H_{13}NOS_2$ (239.35), C, 55.20; H, 5.47; N, 5.85; Found: C, 55.30%; H, 5.40%; N, 5.90%.

4.1.6. *4-Hydroxy-3-propylthiazolidine-2-thione (**3f**)*

Brown oil; yield: 86%.IR (KBr) (υ_{max}, cm^{-1}): 3305, 1455, 1306, 1225, 1100. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 5.64 (dd, $J_1 = 6.4$ Hz, $J_2 = 1.5$ Hz, 1H, CH), 4.16–4.00 and 3.51 (2m, 3H, NCH_2 and OH), 3.65 and 3.18 (AMX system, $\delta_A = 3.65$ and $\delta_M = 3.18$ ppm, $J_{AM} = 12.4$ Hz, $J_{AX} = 6.5$ Hz, and $J_{MX} = 1.7$ Hz, 2H, SCH_2), 1.81–1.66 (m, 2H, CH_3CH_2), 0.96 (t, 3H, $^3J_{HH} = 7.3$ Hz, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$): δ 196.4 (C9S), 89.7 (CH), 48.5 (NCH_2), 36.4 (SCH_2), 20.7 (CH_2CH_3), 11.3 (CH_3). EI-MS (m/z): 177 (M^+, 100), 118 (45), 100 (97), 91 (22). Anal.Calcd for $C_6H_{11}NOS_2$ (177.28): C, 40.65; H, 6.25; N, 7.90; Found: C, 40.60%; H, 6.30%; N, 7.84%.

4.2. *Procedure for the preparation of 3-benzylthiazole-2(3H)-thione (6)*

To a stirred solution of **3a** (2 mmol) in 2 ml of CH_3CN was added 0.1 ml of H_3PO_4. The mixture was refluxed for 2 h. After completion, the solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel (Merck 230–400 mesh) using the *n*-hexane–EtOAc mixture as the eluent (5:1) to afford **6** as white crystals. Yield 90%; mp 99 − 100°C. IR (KBr) (υ_{max}, cm^{-1}): 1370, 1306, 1205, 1135. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.40–7.33 (m, 5H, CH-Ar), 6.94 (d, $^3J_{HH} = 6.0$ Hz, 1H, N*CH* 9CH), 6.57 (d, $^3J_{HH} = 6.0$ Hz, 1H, NCH9 *CH*), 5.38 (s, 2H, NCH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 188.3 (C 9 S), 134.9 (C), 130.8 (N*CH* 9CH), 129.1 (2CH), 128.5 (CH), 128.3 (2CH), 111.1 (NCH9 *CH*), 52.8 (CH_2N). EI-MS (m/z): 207 (M^+, 73), 174 (25), 91 (100), 65 (50). Anal.Calcd for $C_{10}H_9NS_2$ (207.31): C, 57.94; H, 4.38; N, 6.76; Found: C, 57.85; H, 4.41; N, 6.80.

Acknowledgements

We are grateful to Dr Farzad Nikpour for his assistance.

Supplemental data

Supplemental data for this article can be accessed at http://dx.doi.org/10.1080/17415993.2014.907407.

References

[1] Anastas PT, Warner JC. Green chemistry: theory and practice. New York: Oxford University Press; 2000.
[2] Martins MAP, Frizzo CP, Moreira DN, Buriol L, Machado P. Solvent-free heterocyclic synthesis. Chem Rev. 2009;109:4140–4182.
[3] Rudorf W-D. Reactions of carbon disulfide with N-nucleophiles. J Sulfur Chem. 2007;28:295–339.
[4] Kondo T, Mitsudo T-A. Metal-catalyzed carbon-sulfur bond formation. Chem Rev. 2000;100:3205–3220.
[5] Cui Y, Floreancig PE. Synthesis of sulfur-containing heterocycles through oxidative carbon–hydrogen bond functionalization. Org Lett. 2012;14:1720–1723.
[6] Gong Y-D, Lee T. Combinatorial syntheses of five-membered ring heterocycles using carbon disulfide and a solid support. J Comb Chem. 2010;12:393–409.
[7] Nguyen, TB, Tran MQ, Ermolenko L, Al-Mourabit A. Three-component reaction between alkynes, elemental sulfur, and aliphatic mines: a general, straightforward, and atom economical approach to thioamides. Org Lett. 2014;16:310–313.
[8] Cao S-L, Feng, Y-P, Jiang Y-Y, Liu S-Y, Ding G-Y, Li R-T. Synthesis and in vitro antitumor activity of 4 (3*H*)-quinazolinone derivatives with dithiocarbamate side chains. Bioorg Med Chem Lett. 2005;15:1915–1917.

[9] Aboul-Fadl T, Hussein M A, El-Shorbagi A-N, Khallil A-R. New 2*H*-tetrahydro-1,3,5-thiadiazine-2-thiones incorporating glycine and glycinamide as potential antifungal agents. Arch Pharm Pharm Med Chem. 2002;9:438–442.
[10] Jean Jr DJ St, Fotsch C. Mitigating heterocycle metabolism in drug discovery. J Med Chem. 2012;55:6002–6020.
[11] Yonova, IM, Osborne, CA, Morrissette, NS, Jarvo, ER. Diaryl and heteroaryl sulfides: synthesis via sulfonyl chlorides and evaluation as selective anti-breast-cancer agents. J Org Chem. 2014;79:1947–1953.
[12] Lam T, Hilgers MT, Cunningham ML, Kwan BP, Nelson KJ, Brown-Driver V, Ong V, Trzoss M, Hough G, Shaw KJ, Finn J. Structure-based design of new dihydrofolate reductase antibacterial agents: 7-(benzimidazol-1-yl)-2,4-diaminoquinazolines. J Med Chem. 2014;57:651–668.
[13] Nieuwenhuizen PJ, Ehlers AW, Haasnoot JG, Janse SR, Reedijk J, Baerends EJ. The mechanism of zinc (II)-dithiocarbamate-accelerated vulcanization uncovered; theoretical and experimental evidence. J Am Chem Soc. 1999;121:163–168.
[14] Gan S-F, Wan J-P, Pan Y-J, Sun C-R. Water-mediated multicomponent reaction: a facile and efficient synthesis of multisubstituted thiazolidine-2-thiones. Synlett. 2010;973–975.
[15] Tissaoui K, Raouafi N, Boujlel K. Electrogenerated base promoted synthesis of *N*-substituted-4-hydroxy-4-methylthiazolidine-2-thione derivatives. J Chem Res. 2009;11:710–712.
[16] Yavari I, Seyfi S, Hossaini Z, Sabbaghan M, Shirgahi-Talari F. Efficient synthesis of 2-thioxo-1,3-thiazolanes from primary amines, CS_2, and ethyl bromopyruvate. Monatsh Chem. 2008;139:1479–1482.
[17] Rothman JH. Direct and facile syntheses of heterocyclic vinyl-*C*-nucleosides for recognition of inverted base pairs by DNA triple helix formation: first report by direct Wittig route. J Org Chem. 2007;10:3945–3948.
[18] Chiba T, Sato H, Kato T. Synthesis of ethyl 2-thioxo (and 2-methylene) thiazoline-4-acetates. Chem Pharm Bull. 1982;10:3548–3554.
[19] Lamon RW, Humphlett WJ. 4-Thiazoline-2-thiones. IV. Preparation from amino acids. J Heterocycl Chem. 1967;4:605–609.
[20] Roschester J, Sandström J. Conformational analysis of *N*-(1-methoxycarbonylethyl)-Δ^4-thiazoline-2-thiones by temperature-dependent circular dichroism and NMR spectroscopy and by molecular mechanics calculations.Tetrahedron. 1989;45:5081–5100.
[21] Safaei-Ghomi J, Salimi F, Ramazani A, Zeinali Nasrabadi F, Ahmadi Y. The reaction of carbon disulfide with bromoacetophenone in the presence of primary amines: synthesis of 3-alkyl-4-phenyl-1,3-thiazole-2(3*H*)-thione derivatives. J Sulfur Chem. 2012;33:87–92.
[22] Azizi N, Aryanasab F, Torkiyan L, Ziyaei A, Saidi MR. One-pot synthesis of dithiocarbamates accelerated in water. J Org Chem. 2006;71:3634–3635.
[23] Alizadeh A, Rostamnia S, Zohreh N, Hosseinpour R. A simple and effective approach to the synthesis of rhodanine derivatives via three-component reactions in water. Tetrahedron Lett. 2009;50:1533–1535.