Three-component and one-pot reaction between phenacyl bromide and primary amines in the presence of carbon disulfide

Alireza Hassanabadi* and Khatereh Khandan-Barani

Department of Chemistry, Islamic Azad University, Zahedan Branch, PO Box 98135-978, Zahedan, Iran

A three-component and one-pot reaction between phenacyl bromide and primary amines in the presence of carbon disulfide to afford substituted 4-hydroxy-4-phenylthiazolidine-2-thiones in high yields.

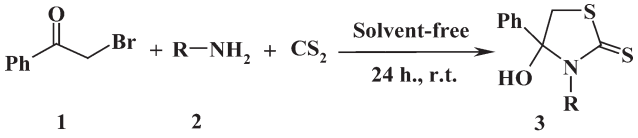
Keywords: thiazolidine-2-thiones, phenacyl bromide, carbon disulfide, primary amines

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion.[1–4] Dithiocarbamates have received considerable attention due to their numerous biological activities.[5–8] their pivotal role in agriculture,[9–11] and as linkers in solid-phase organic synthesis.[12–14] Dithiocarbamates are also widely used in medicinal chemistry and have found application in the treatment of cancer.[15,16] Therefore, synthesis of these compounds has received considerable attention. General methods for their synthesis involve the reaction of an amine with costly and toxic reagents, such as thiophosgene or isothiocyanate.[17] As a part of our current studies on the development of new routes in organic synthesis,[18–21] we report here an efficient one-pot synthesis of thiazolidine-2-thiones employing readily available starting materials.

Results and discussion

Reaction between phenacyl bromide **1** and primary amines **2** in the presence of carbon disulfide to afford the thiazolidine-2-thiones **3** in high yields (Scheme 1).

The structures of compounds **3a–g** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Because of the presence of an estereogenic centre in these molecules, the hydrogen atoms of the CH_2 group are diastereotopic.



1 2 3

2, 3	R	*Yield%
a	C_6H_5	83
b	4-Me C_6H_4	85
c	4-$NO_2C_6H_4$	80
d	4-Br C_6H_4	82
e	$C_6H_5CH_2$	84
f	n-Bu	80
g	CH_3	81

* Isolated yields

Scheme 1 Three-component reaction between carbon disulfide, primary amines and phenacyl bromide.

For example, the ^{1}H NMR spectrum of **3a** exhibited a single line was observed at $\delta = 5.22$ which arises from the OH proton and disappeared by addition of D_2O to the $CDCl_3$ solution of **3a**. Since compounds **3** possess one stereogenic centre, the hydrogen atoms of the CH_2 group are diastereotopic. Thus they resonate as an AB-quartet. Aromatic protons resonate between 6.85 and 7.52 ppm as multiplets. The C=S group resonance in ^{13}C NMR spectra of **3a** appears at 197.2 ppm. The ^{13}C NMR spectrum of **3a** showed 11 distinct resonances in agreement with the proposed structure. The mass spectrum of **3a** displayed the molecular ion peak at *m/z* = 287. The IR spectrum of compound **3a** also supported the suggested structure, strong absorption bands were observed at 3234 cm^{-1} for the OH group. A tentative mechanism for this transformation is proposed in Scheme 2.

It is reasonable to assume that compound **4** results from the initial addition of carbon disulfide to the primary amines **2**, which react with phenacyl bromide **1** to produce **5**. Intermediate **5** undergoes HBr elimination and cyclisation reaction to generate **3**.

We now report the three-component reaction between phenacyl bromide and primary amines in the presence of carbon disulfide to afford the thiazolidine-2-thiones in good yields. This method has the advantage that the reaction is performed in neutral conditions and the starting materials can be mixed without any activation nor modification.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyser. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C spectra were recorded on Bruker DRX-500 Avance spectrometer in $CDCl_3$ using TMS as the internal standard or 85% H_3PO_4 as the external standard. Chemicals were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

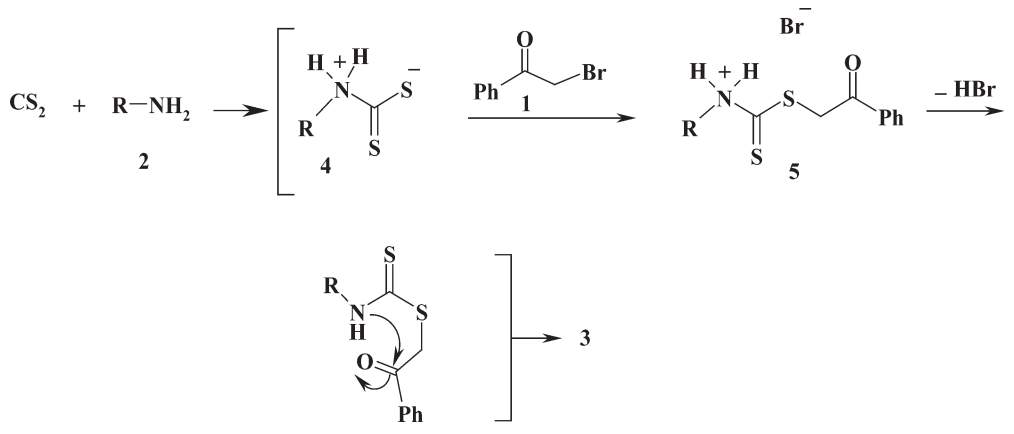
General procedure

Primary amine (1 mmol) was added dropwise to a magnetically stirred solution of phenacyl bromide (1 mmol) and carbon disulfide (5 mmol) at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane-ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product.

4-Hydroxy-3,4-diphenyl-thiazolidine-2-thione (**3a**):Yellow powder, m.p. 137–139 °C, IR (KBr) (ν_{max} cm^{-1}): 3234, 1617, 1518, 1160, 1102. Anal. Calcd for $C_{15}H_{13}NOS_2$: C, 62.69; H, 4.56; N, 4.87. Found: C, 62.80; H, 4.43; N, 4.75%. MS (*m/z*, %): 287 (8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.28 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 4.40 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 5.22 (1H, s, OH), 6.85–7.52 (10H, m, 10 CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 35.1 (CH_2), 91.8 (C), 114.1, 119.3, 126.5, 127.2, 128.4, 129.7, 145.4 and 146.5 (aromatic moiety), 197.2 (C=S) ppm.

3-(p-Tolyl)-4-hydroxy-4-phenyl-thiazolidine-2-thione (**3b**): Yellow powder, m.p. 132–134 °C, IR (KBr) (ν_{max} cm^{-1}): 3230, 1614, 1511, 1165, 1108. Anal. Calcd for $C_{16}H_{15}NOS_2$: C, 63.76; H, 5.02; N, 4.65.

* Correspondent. E-mail: ar_hasanabadi@yahoo.com



Scheme 2 Suggested mechanism for formation of compound **3**.

Found: C, 63.90; H, 5.15; N, 4.54%. MS (*m/z*, %): 301 (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (3H, s, Me), 3.95 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 4.15 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 4.98 (1H, s, OH), 7.05 (2H, d, $^3J_{HH}$= 8.1 Hz, 2CH), 7.24 (2H, d, $^3J_{HH}$= 8.1 Hz, 2CH), 7.32–7.46 (5H, m, 5CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.9 (CH_3), 36.9 (CH_2), 93.8 (C), 122.1, 126.4, 127.5, 129.3, 129.6, 133.5, 136.5 and 146.2 (aromatic moiety), 198.4 (C=S) ppm.

3-(4-Nitrophenyl)-4-hydroxy-4-phenyl-thiazolidine-2-thione (**3c**): Yellow powder, m.p. 140–142 °C, IR (KBr) (ν_{max} cm^{-1}): 3238, 1617, 1542, 1510, 1367, 1162, 1101. Anal. Calcd for $C_{15}H_{12}N_2O_3S_2$: C, 54.20; H, 3.64; N, 8.43. Found: C, 54.28; H, 3.50; N, 8.53%. MS (*m/z*, %): 332 (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 4.35 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 5.17 (1H, s, OH), 7.56 (2H, d, $^3J_{HH}$= 8.1 Hz, 2CH), 8.22 (2H, d, $^3J_{HH}$= 8.1 Hz, 2CH), 7.3–7.40 (5H, m, 5CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 37.4 (CH_2), 94.6 (C), 119.8, 125.1, 126.2, 127.4, 129.3, 142.6, 146.2 and 148.7 (aromatic moiety), 198.8 (C=S) ppm.

3-(4-Bromophenyl)-4-hydroxy-4-phenyl-thiazolidine-2-thione (**3d**): Yellow powder, m.p. 121–123 °C, IR (KBr) (ν_{max} cm^{-1}): 3218, 1605, 1514, 1162, 1100. Anal. Calcd for $C_{15}H_{12}BrNOS_2$: C, 49.19; H, 3.30; N, 3.82. Found: C, 49.30; H, 3.38; N, 3.71%. MS (*m/z*, %): 366 (4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 4.46 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 5.74 (1H, s, OH), 6.52 (2H, d, $^3J_{HH}$= 8.1 Hz, 2CH), 7.64 (2H, d, $^3J_{HH}$= 8.1 Hz, 2CH), 7.14–7.52 (5H, m, 5CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 37.1 (CH_2), 94.5 (C), 119.4, 125.7, 126.4, 127.5, 129.3, 129.6, 135.6 and 145.7 (aromatic moiety), 198.5 (C=S) ppm.

3-Benzyl-4-hydroxy-4-phenyl-thiazolidine-2-thione (**3e**): White powder, m.p. 115–117 °C, IR (KBr) (ν_{max} cm^{-1}): 3205, 1598, 1487, 1152. Anal. Calcd for $C_{16}H_{15}NOS_2$: C, 63.76; H, 5.02; N, 4.65. Found: C, 63.90; H, 5.15; N, 4.54%. MS (*m/z*, %): 301 (10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.38 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 3.67 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 4.42 (1H, d, $^2J_{HH}$ = 15.5 Hz, CH), 5.03 (1H, s, OH), 5.44 (1H, d, $^2J_{HH}$ = 15.5 Hz, CH), 7.14–7.95 (10H, m, 10 CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 37.2 (CH_2), 48.4 (CH_2), 94.5 (C), 126.4, 127.3, 127.8, 128.3, 128.9, 129.5, 135.3 and 145.7 (aromatic moiety), 198.6 (C=S) ppm.

3-Butyl-4-hydroxy-4-phenyl-thiazolidine-2-thione (**3f**): Yellow powder, m.p. 112–114 °C, IR (KBr) (ν_{max} cm^{-1}): 3226, 1612, 1535, 1190, 1152. Anal. Calcd for $C_{13}H_{17}NOS_2$: C, 58.39; H, 6.41; N, 5.24. Found: C, 58.50; H, 6.55; N, 5.11%. MS (*m/z*, %): 267 (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (2H, m, CH_2), 1.44 (3H, t, $^3J_{HH}$= 7.05 Hz, CH_3), 1.51 (2H, m, CH_2), 3.07 (1H, m, CHN), 3.36 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 3.70 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 3.78 (1H, m, CHN), 5.67 (1H, s, OH), 7.28–7.55 (5H, m, 5 CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.1 (CH_3), 19.3 (CH_2), 29.3 (CH_2), 37.6 (CH_2), 41.1 (NCH_2), 95.4 (C), 126.8, 127.5, 129.1 and 146.2 (aromatic moiety), 196.7 (C=S) ppm.

3-Methyl-4-hydroxy-4-phenyl-thiazolidine-2-thione (**3g**): Yellow powder, m.p. 116–118 °C, IR (KBr) (ν_{max} cm^{-1}): 3195, 1610, 1537, 1196, 1158. Anal. Calcd for $C_{10}H_{11}NOS_2$: C, 53.30; H, 4.92; N, 6.22. Found: C, 53.22; H, 4.80; N, 6.15%. MS (*m/z*, %): 225 (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.94 (3H, s, CH_3N), 3.34 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 3.72 (1H, d, $^2J_{HH}$ = 11.5 Hz, CH), 5.60 (1H, s, OH), 7.31–7.62 (5H, m, 5CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.5 (NCH_3), 37.4 (CH_2), 95.1 (C), 126.7, 127.7, 129.3 and 146.1 (aromatic moiety), 196.4 (C=S) ppm.

We gratefully acknowledge financial support from the Research Council of Islamic Azad University of Zahedan of Iran.

Received 28 October 2012; accepted 5 December 2012
Paper 1201593 *doi: 10.3184/174751912X13568926198645*
Published online: 13 February 2013

References

1 A. Dömling, *Chem. Rev*., 2006, **106**, 17.
2 C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51.
3 J. Zhu, *Eur. J. Org. Chem.*, 2003, **2003**, 1133.
4 A, Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3168.
5 E. D, Caldas, M. Hosana Conceicao, M.C.C. Miranda, L. Souza and J.F. Lima, *J. Agric.Food Chem.*, 2001, **49**, 4521.
6 A.W. Erian and S.M. Sherif, *Tetrahedron*, 1999, **55**, 7957.
7 M. Beji, H. Sbihi, A. Baklouti andA. Cambon, *J. Fluor. Chem.*, 1999, **99**, 17.
8 A. Goel, S.J. Mazur, R.J. Fattah, T.L. Hartman, J.A. Turpin, M. Huang, W.G. Rice, E. Appella and J.K. Inman, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 767.
9 T. Mizuno, I. Nishiguchi, T. Okushi and T. Hirashima, *Tetrahedron Lett*., 1991, **32**, 6867
10 C. Rafin, E. Veignie, M. Sancholle, D. Postal, C. Len, P. Villa and G. Ronco, *J. Agric. Food Chem.*, 2000, **48**, 5283.
11 C. Len, D. Postal, G. Ronco, P. Villa, C. Goubert, E. Jeufrault, B. Mathon and H. Simon, *J. Agric. Food Chem.*, 1997, **45**, 3.
12 P. Morf, F. Raimondi, H.G. Nothofer, B. Schnyder, A. Yasuda, J.M. Wessels and T.A. Jung, *Langmuir*, 2006, **22**, 658.
13 A. McClain and Y.L. Hsieh, *J. Appl. Polym. Sci.*, 2004, **92**, 218.
14 A.D. Dunn and W.D. Rudorf, *Carbon disulphide in organic chemistry*. Ellis Harwood, Chichester, 1989, p. 226.
15 L. Ronconi, C. Marzano, P. Zanello, M. Corsini, G. Miolo, C. Macca, A. Trevisan and D. Fregona, *J. Med. Chem.*, 2006, **49**, 1648.
16 G.H. Elgemeie and S.H. Sayed, *Synthesis*, 2001, 1747.
17 W. Chin-Hsien, *Synthesis*, 1981, 622.
18 M.H. Mosslemin, M. Anary-Abbasinejad, A. Hassanabadi and M.A. Bagheri, *J. Sulfur. Chem*., 2010, **31**, 135.
19 A. Hassanabadi, M.H. Mosslemin and S.E. Tadayonfar, *J. Chem. Res*., 2011, **35**, 29.
20 A. Hassanabadi, M.H. Mosslemin, M. Anary-Abbasinejad, M.R. Hosseini-Tabatabaei, H. Mahmoudian and S.E. Tadayonfar, *J. Sulfur. Chem*., 2011, **32**, 355.
21 R. Mohebat, M.H. Mosslemin, A. Dehghan-Darehshiri and A. Hassanabadi, *J. Sulfur. Chem*., 2011, **32**, 557.