Monatsh Chem 139, 1479–1482 (2008)
DOI 10.1007/s00706-008-0953-x
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Efficient synthesis of 2-thioxo-1,3-thiazolanes from primary amines, CS_2, and ethyl bromopyruvate

Issa Yavari, Samereh Seyfi, Zinatossadat Hossaini, Maryam Sabbaghan, Faezeh Shirgahi-Talari

Chemistry Department, Tarbiat Modares University, Tehran, Iran

Received 16 April 2008; Accepted 22 April 2008; Published online 9 July 2008

Abstract An efficient synthesis of 2-thioxo-1,3-thiazolanes is described *via* reaction of carbon disulfide, ethyl bromopyruvate, and primary amines.

Keywords 1,3-Thiazolane; Benzylamine; Ethyl bromopyruvate; Carbon disulfide; Primary amines.

Introduction

During the last few decades, a central objective in synthetic organic chemistry has been to develop efficient syntheses of biologically active compounds with potential application in the pharmaceutical or agrochemical industries. In this context, the solvent-free approach is simple with amazing versatility. The reactions occur under mild conditions and usually require easier work-up procedures and simpler equipment. Moreover, it may allow access to compounds that require harsh reaction conditions under traditional approaches or when the yields are too low to be of practical convenience [1–3]. Dithiocarbamates have received considerable attention due to their numerous biological activities [4–7] and their pivotal role in agriculture [8–10], and as linkers in solid-phase organic synthesis [11–13]. Dithiocarbamates are also widely used in medicinal chemistry and have found application in the treatment of cancer [14, 15].

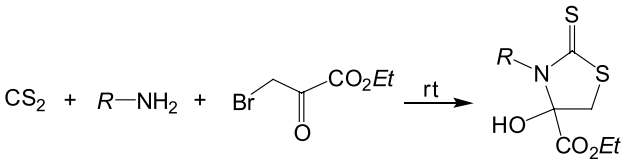
Correspondence: Issa Yavari, Chemistry Department, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran. E-mail: yavarisa@modares.ac.ir

Therefore, synthesis of these compounds received considerable attention. General methods for their synthesis involve the reaction of an amine with costly and toxic reagents, such as thiophosgene or isothiocyanate [16]. As part of our current studies on the development of new routes in heterocyclic synthesis [17–20], we describe an efficient procedure for the direct synthesis of functionalized cyclic thiocarbamates from the reaction of CS_2 and ethyl bromopyruvate (**2**) in the presence of primary amines **1** at room temperature (Scheme 1).

Results and discussion

The reaction of **1** with **2** in the presence of CS_2 led to 2-thioxo-1,3-thiazolanes **3** in 80–90% yields (Scheme 1). Structures of compounds **3a**–**3i** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. Because of the presence of an estereogenic center in these molecules, the hydrogen atoms of the CH_2 and OCH_2 groups are diastereotopic. Thus, the ^{1}H NMR spectra of **3a**–**3i** exhibited characteristic multiplets for CH_2 and OCH_2 moieties. The carbonyl and thiocarbonyl resonances in the ^{13}C NMR spectra of **3a**–**3i** appear at about 170 (C=O) and 198 (C=S) ppm. The mass spectra of these compounds displayed the molecular ion peak at appropriate m/z values.

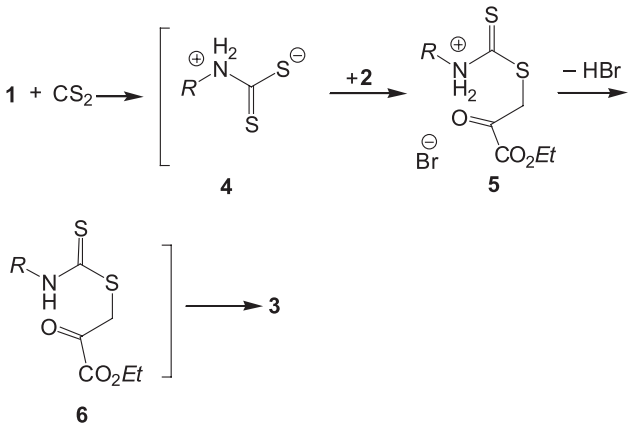
A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of the 1:1 adducts **4**



1 2 3

1,3	R	Yield/% of 3
a	*n*-Bu	86
b	CH_2CH_2OH	86
c	*Bn*	90
d	2-Cl-*Bn*	75
e	4-*Me*-*Bn*	85
f	4-Cl-*Bn*	85
g	4-*Me*O-*Bn*	80
h	2-Naphthyl-CH_2	87
i	*Ph*	83

Scheme 1



Scheme 2

from CS_2 and amine **1**, which are subsequently attacked by ethyl bromopyruvate to produce **5**. Intermediate **5** undergoes HBr elimination and cyclization reaction to generate **3**.

In conclusion, the reaction of primary alkyl amines with CS_2 in the presence of ethyl bromopyruvate led to 2-thioxo-1,3-thiazolanes in excellent yields. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Experimental

Compounds **1**, **2**, and CS_2 were obtained from Fluka and used without further purification. Mp Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer; in cm^{-1}. ^1H and ^{13}C NMR Spectra: Bruker DRX-500-Avance instrument; in $CDCl_3$ at 500.1 and 125.7 MHz; δ in ppm, J in Hz. EI-MS (70 eV): Finnigan MAT-8430 mass spectrometer; m/z. Elemental analyses (C, H, and N): *Heraeus* CHN-O-Rapid analyzer; the results were in good agreement with the calculated values.

General procedure for the preparation of compounds ***3***

Primary amine **1** (2 mmol) was added to a mixture of 0.76 g CS_2 (10 mmol) and 0.39 g ethyl bromopyruvate **2** (2 mmol) at rt. The reaction mixture was then stirred for 12 h. The product was separated by column chromatography (SiO_2; *n*-hexane/*Ac*O*Et* 10/1) to afford the pure title compounds.

Ethyl 3-butyl-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3a**, $C_{10}H_{17}NO_3S_2$)

Pale yellow powder, mp 125–127°C, yield 0.45 g (86%); IR (KBr): $\bar{\nu} = 3224$, 1738, 1614, 1531, 1430, 1334, 1194, 1157 cm^{-1}; EI-MS: m/z (%) = 263 (M^+, 5), 115 (85), 148 (56), 147 (32), 57 (100), 45 (48); ^1H NMR: $\delta = 0.89$ (3H, t, $^3J = 7.4$ Hz, *Me*), 1.23–1.29 (2H, m, CH_2), 1.32 (3H, *t*, $^3J = 7.2$ Hz, *Me*), 1.47–1.50 (1H, m, CH), 1.63–1.66 (1H, m, CH), 3.33 (1H, d, $^2J = 12.0$ Hz, CH), 3.36–3.42 (1H, m, CH), 3.58–3.66 (1H, m, CH), 3.67 (1H, d, $^2J = 12.0$ Hz, CH), 4.15–4.37 (2H, m, OCH_2), 5.75 (1H, s, OH) ppm; ^{13}C NMR: $\delta = 13.4$ (*Me*), 13.8 (*Me*), 20.0 (CH_2), 29.2 (CH_2), 37.8 (CH_2), 46.1 (CH_2), 64.2 (OCH_2), 95.9 (C), 169.6 (C=O), 196.8 (C=S) ppm.

Ethyl 3-(2-hydroxyethyl)-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3b**, $C_8H_{13}NO_4S_2$)

Pale yellow powder, mp 116–118°C, yield 0.43 g (86%); IR (KBr): $\bar{\nu} = 3192$, 1740, 1588, 1489, 1439, 1354, 1185, 1200 cm^{-1}; EI-MS: m/z (%) = 251 (M^+, 15), 149 (86), 135 (64), 103 (65), 73 (95), 45 (100); ^1H NMR: $\delta = 1.36$ (3H, t, $^3J = 7.2$ Hz, *Me*), 3.33 (1H, d, $^2J = 11.0$ Hz, CH), 3.69–3.74 (2H, m, NCH_2), 3.79 (1H, d, $^2J = 11.0$ Hz, CH), 3.94–3.99 (1H, m, CH), 4.25–4.30 (1H, m, CH), 4.32–4.36 (2H, m, OCH), 4.56 (1H, s, OH), 4.67 (1H, t, $^3J = 5.3$ Hz, OH) ppm; ^{13}C NMR: $\delta = 14.0$ (*Me*), 38.2 (CH_2), 48.9 (CH_2), 59.2 (OCH_2), 63.6 (OCH_2), 96.4 (C), 168.6 (C=O), 198.5 (C=S) ppm.

Ethyl 3-benzyl-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3c**, $C_{13}H_{15}NO_3S_2$)

Colorless crystals, mp 120–122°C, yield 0.53 g (90%); IR (KBr): $\bar{\nu} = 3200$, 1747, 1591, 1483, 1431, 1342, 1204, 1151 cm^{-1}; EI-MS: m/z (%) = 297 (M^+, 38), 181 (40), 149 (78), 148 (94), 91 (100), 77 (46), 45 (68); ^1H NMR: $\delta = 1.00$ (3H, t, $^3J = 7.2$ Hz, *Me*), 3.33 (1H, d, $^2J = 12.0$ Hz, CH), 3.31–3.38 (1H, m, CH), 3.70 (1H, d, $^2J = 12.0$ Hz, CH), 3.86–3.92 (1H, m, CH), 4.41 (1H, d, $^2J = 15.4$ Hz, CH), 4.97 (1H, s, OH), 5.46 (1H, d, $^2J = 12.0$ Hz, CH), 7.23–7.26 (3H, m, 3CH), 7.31 (2H, d, $^3J = 7.5$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.5$ (*Me*), 37.9 (CH_2), 48.3 (CH_2), 64.2 (OCH_2), 94.8 (C), 127.9 (CH), 128.3 (2CH), 128.7 (2CH), 135.1 (C), 169.5 (C=O), 198.8 (C=S) ppm.

Ethyl 3-(2-chlorobenzyl)-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3d**, $C_{13}H_{14}ClNO_3S_2$)
Pale yellow powder, mp 163–165°C, yield 0.49 g (75%); IR (KBr): $\bar{\nu} = 3215$, 1738, 1489, 1471, 1429, 1340, 1395, 1145 cm^{-1}; EI-MS: m/z (%) = 331 (M^+, 15), 182 (75), 149 (56), 125 (64), 112 (45), (84); ^1H NMR: $\delta = 1.12$ (3H, t, $^3J = 7.2$ Hz, *Me*), 3.42 (1H, d, $^2J = 12.1$ Hz, CH), 3.64–3.71 (1H, m, CH), 3.81 (1H, d, $^2J = 12.1$ Hz, CH), 3.96–4.05 (1H, m, CH), 4.90 (1H, d, $^2J = 16.4$ Hz, CH), 5.04 (1H, s, OH), 5.21 (1H, d, $^2J = 16.4$ Hz, CH), 7.19 (2H, t, $^3J = 7.6$ Hz, 2CH), 7.32 (1H, d, $^3J = 7.5$ Hz, CH), 7.38 (1H, d, $^3J = 7.6$ Hz, CH) ppm; ^{13}C NMR: $\delta = 13.5$ (*Me*), 37.8 (CH_2), 45.6 (CH_2), 64.2 (OCH_2), 95.2 (C), 126.5 (CH), 128.7 (CH), 129.2 (CH), 129.3 (CH), 132.3 (C), 132.7 (C), 169.0 (C=O), 198.9 (C=S) ppm.

Ethyl 3-(4-methylbenzyl)-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3e**, $C_{14}H_{17}NO_3S_2$)
Pale yellow powder, mp 129–131°C, yield 0.53 g (85%); IR (KBr): $\bar{\nu} = 3195$, 1741, 1590, 1481, 1433, 1345, 1200, 1150 cm^{-1}; EI-MS: m/z (%) = 311 (M^+, 15); 162 (85), 149 (45), 105 (100), 91 (44), 45 (68); ^1H NMR: $\delta = 1.05$ (3H, t, $^3J = 7.2$ Hz, *Me*), 2.31 (3H, s, *Me*), 3.35 (1H, d, $^2J = 12.0$ Hz, CH), 3.43–3.46 (1H, m, CH), 3.70 (1H, d, $^2J = 12.0$ Hz, CH), 3.93–3.97 (1H, m, CH), 4.45 (1H, d, $^2J = 15.2$ Hz, CH), 4.94 (1H, s, OH), 5.42 (1H, d, $^2J = 15.2$ Hz, CH), 7.08 (2H, d, $^3J = 8.1$ Hz, 2CH), 7.23 (2H, d, $^3J = 8.1$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.9$ (*Me*), 21.0 (*Me*), 37.8 (CH_2), 48.1 (CH_2), 64.1 (OCH_2), 94.7 (C), 128.7 (2CH), 128.9 (2CH), 132.0 (C), 137.6 (C), 169.6 (C=O), 198.6 (C=S) ppm.

Ethyl 3-(4-chlorobenzyl)-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3f**, $C_{13}H_{14}ClNO_3S_2$)
Pale yellow crystals, mp 153–155°C, yield 0.56 g (85%); IR (KBr): $\bar{\nu} = 3220$, 1745, 1589, 1480, 1430, 1339, 1201, 1152 cm^{-1}; EI-MS: m/z (%) = 331 (M^+, 10), 182 (85), 149 (57), 125 (100), 111 (85), 45 (62); ^1H NMR: $\delta = 1.08$ (3H, t, $^3J = 7.2$ Hz, *Me*), 3.37 (1H, d, $^2J = 12.0$ Hz, CH), 3.51–3.58 (H, m, CH), 3.72 (1H, d, $^2J = 12.0$ Hz, CH), 3.97–4.04 (1H, m, CH), 4.47 (1H, d, $^2J = 15.5$ Hz, CH), 4.93 (1H, s, OH), 5.35 (1H, d, $^2J = 15.5$ Hz, CH), 7.23 (2H, d, $^3J = 7.8$ Hz, 2CH), 7.29 (2H, d, $^3J = 7.8$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.5$ (*Me*), 37.9 (CH_2), 47.6 (CH_2), 64.3 (OCH_2), 94.7 (C), 128.3 (2CH), 129.9 (2CH), 133.7 (C), 133.8 (C), 169.5 (C=O), 198.8 (C=S) ppm.

Ethyl 3-(4-methoxybenzyl)-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3g**, $C_{14}H_{17}NO_4S_2$)
Pale yellow powder, mp 150–152°C, yield 0.52 g (80%); IR (KBr): $\bar{\nu} = 3219$, 1744, 1584, 1475, 1395, 1335, 1198, 1149 cm^{-1}; EI-MS: m/z (%) = 327 (M^+, 5), 178 (85), 149 (66), 121 (64), 107 (85), 45 (62); ^1H NMR: $\delta = 1.05$ (3H, t, $^3J = 7.2$ Hz, *Me*), 3.31 (1H, d, $^2J = 12.0$ Hz, CH), 3.46–3.49 (1H, m, CH), 3.67 (1H, d, $^2J = 12.0$ Hz, CH), 3.76 (3H, s, *Me*O), 3.94–3.97 (1H, m, CH), 4.41 (1H, d, $^2J = 15.2$ Hz, CH), 4.98 (1H, s, OH), 5.39 (1H, d, $^2J = 15.4$ Hz, CH), 6.81 (2H, d, $^3J = 8.2$ Hz, 2CH), 7.27 (2H, d, $^3J = 8.2$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.5$ (*Me*), 37.9 (CH_2), 47.8 (CH_2), 55.3 (*Me*O), 64.2 (OCH_2), 94.8 (C), 113.7 (2CH), 127.2 (C), 130.1 (2CH), 159.3 (C), 169.6 (C=O), 198.5 (C=S) ppm.

Ethyl 3-(1-naphthylmethyl)-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3h**, $C_{17}H_{17}NO_3S_2$)
Pale yellow powder, mp 124–126°C, yield 0.60 g (87%); IR (KBr): $\bar{\nu} = 3214$, 1720, 1601, 1512, 1410, 1340, 1225, 1100 cm^{-1}; EI-MS: m/z (%) = 347 (M^+, 10), 206 (54), 199 (58), 141 (100), 127 (48), 45 (84); ^1H NMR: $\delta = 1.12$ (3H, t, $^3J = 7.2$ Hz, *Me*), 3.45 (1H, d, $^2J = 11.9$ Hz, CH), 3.56–3.64 (1H, m, CH), 3.80 (1H, d, $^2J = 11.9$ Hz, CH), 3.94–4.00 (1H, m, CH), 5.01 (1H, d, $^2J = 15.2$ Hz, CH), 5.89 (1H, s, OH), 5.27 (1H, d, $^2J = 15.2$ Hz, CH), 6.68 (1H, t, $^3J = 7.2$ Hz, CH), 7.36 (1H, t, $^3J = 7.5$ Hz, CH), 7.56 (1H, t, $^3J = 7.6$ Hz, CH), 7.60 (1H, t, $^3J = 7.5$ Hz, CH), 7.75 (1H, d, $^3J = 7.6$ Hz, CH), 7.88 (1H, d, $^3J = 7.6$ Hz, CH), 8.07 (1H, t, $^3J = 7.5$ Hz, CH) ppm; ^{13}C NMR: $\delta = 13.8$ (*Me*), 35.4 (CH_2), 49.3 (CH_2), 64.2 (OCH_2), 94.8 (C), 121.6 (CH), 122.5 (CH), 125.2 (CH), 125.9 (CH), 126.3 (C), 126.4 (CH), 127.7 (CH), 128.8 (CH), 133.7 (C), 134.0 (C), 169.2 (C=O), 197.1 (C=S) ppm.

Ethyl 3-phenyl-4-hydroxy-2-thioxo-1,3-thiazolane-4-carboxylate (**3i**, $C_{12}H_{13}NO_3S_2$)
Pale yellow powder, mp 134–136°C, yield 0.58 g (83%); IR (KBr): $\bar{\nu} = 3196$, 1734, 1620, 1524, 1500, 1314, 1162, 1104 cm^{-1}; EI-MS: m/z (%) = 283 (M^+, 5), 206 (65), 135 (86), 148 (66), 77 (100), 45 (84); ^1H NMR: $\delta = 1.30$ (3H, t, $^3J = 7.2$ Hz, *Me*), 4.18–4.29 (2H, m, OCH_2), 4.31 (1H, d, $^2J = 11.5$ Hz, CH), 4.41 (1H, d, $^2J = 11.5$ Hz, CH), 6.81 (2H, t, $^3J = 8.2$ Hz, 2CH), 7.00 (1H, s, OH), 7.18 (1H, t, $^3J = 8.2$ Hz, CH), 7.45 (2H, d, $^3J = 8.2$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 14.2$ (*Me*), 35.6 (CH_2), 61.6 (OCH_2), 92.4 (C), 115.3 (2CH), 119.1 (CH), 128.9 (2CH), 145.8 (C), 166.8 (C=O), 197.8 (C=S) ppm.

References

1. Fringuelli F, Girotti R, Pizzo F, Vaccaro L (2006) Org Lett 8:2487
2. Yusubov MS, Wirth T (2005) Org Lett 7:519
3. Shibahara F, Nozaki K, Hiyama TJ (2003) J Am Chem Soc 125:8555
4. Caldas ED, Hosana Conceicüa M, Miranda MCC, Souza L, Lima JF (2001) J Agric Food Chem 49:4521
5. Erian AW, Sherif SM (1999) Tetrahedron 55:7957
6. Beji M, Sbihi H, Baklouti A, Cambon A (1999) J Fluorine Chem 99:17
7. Goel A, Mazur SJ, Fattah RJ, Hartman TL, Turpin JA, Huang M, Rice WG, Appella E, Inman JK (2002) Bioorg Med Chem Lett 12:767
8. Mizuno T, Nishiguchi I, Okushi T, Hirashima T (1991) Tetrahedron Lett 32:6867
9. Rafin C, Veignie E, Sancholle M, Postal D, Len C, Villa P, Ronco G (2000) J Agric Food Chem 48:5283
10. Len C, Postal D, Ronco G, Villa P, Goubert C, Jeufrault E, Mathon B, Simon H (1997) J Agric Food Chem 45:3

11. Morf P, Raimondi F, Nothofer HG, Schnyder B, Yasuda A, Wessels JM, Jung TA (2006) Langmuir 22:658
12. McClain A, Hsieh YL (2004) J Appl Polym Sci 92:218
13. Dunn AD, Rudorf WD (1989) Carbon Disulphide in Organic Chemistry. Ellis Harwood, Chichester, UK, p 226
14. Ronconi L, Marzano C, Zanello P, Corsini M, Miolo G, Macca C, Trevisan A, Fregona D (2006) J Med Chem 49:1648
15. Elgemeie GH, Sayed SH (2001) Synthesis:1747
16. Chin-Hsien W (1981) Synthesis:622
17. Yavari I, Hosseini N, Moradi L (2008) Monatsh Chem 139:133
18. Yavari I, Zare H (2007) Monatsh Chem 138:787
19. Yavari I, Hossaini Z, Sabbaghan M, Ghazanfarpour-Darjani M (2007) Monatsh Chem 138:677
20. Habibi H, Mousavifar L, Yavari I, Yazdanbakhsh MR (2007) Monatsh Chem 138:603