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ORIGINAL PAPER

A one-pot synthesis of *N*-alkylthiazoline-2-thiones from CS_2, primary amines, and 2-chloro-1,3-dicarbonyl compounds in water

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Abstract A simple synthesis of *N*-alkylthiazoline-2-thiones by reaction of primary amines, carbon disulfide, and 2-chloro-1,3-dicarbonyl compounds in water is described. Proceeding without catalyst under one-pot conditions in high yields and with broad scope, this method high synthetic utility.

Keywords *N*-Alkylthiazoline-2-thione · Primary amine · Carbon disulfide · 2-Chloro-1,3-dicarbonyls

Introduction

Thiazoline-2-thiones are an important class of heterocyclic compounds. They are used as powerful ligands, which react with copper(II) chloride and bromide [1] and silver(I) bromide [2]. *N*-Alkylthiazoline-2-thiones are precursors in the synthesis of some electron-rich olefins, which are used as readily accessible cation radical species and act as a molecular conductors [3, 4]. In addition, *N*-alkylthiazoline-2-thiones are used as a diffusion transfer color photographic materials [5].

Synthesis of *N*-alkylthiazoline-2-thiones by treatment of alkylammonium dithiocarbamates with α-haloketones followed by cyclization and dehydration in the presence of an acid has been reported [3, 6–9]. Ethyl 3-alkyl-4-hydroxy-2-thioxothiazolidine-4-carboxylates have been prepared in excellent yields by reaction of the corresponding primary amines with carbon disulfide and ethyl 3-bromo-2-oxopropanoate in the presence of anhydrous potassium phosphate in DMF at room temperature [10]. Recently we described a synthesis of ethyl 3-alkyl-4-oxo-2-thioxo-1,3-thiazolane-5-carboxylates by reaction of primary amines with CS_2 in the presence of diethyl 2-chloromalonate [11]. In this paper, a simple synthesis of *N*-alkylthiazoline-2-thiones by reaction of primary amines, carbon disulfide, and 2-chloro-1,3-dicarbonyl compounds in water is described; the reaction is a development of the pathway reported by Lamon and Humphlett as a three-component procedure in water (Scheme 1). This new catalyst-free, one-pot synthetic method seems facile; the work-up procedure is easy and gives pure target compounds containing several potential centers for further modification.

Results and discussion

The reaction of primary amines, carbon disulfide, and 2-chloro-1,3-dicarbonyl compounds in water produced *N*-alkylthiazoline-2-thiones **3** in high yields. The structures of compounds **3a**–**3i** were apparent from elemental analysis, mass, IR, and NMR spectra. Mass spectra, in particular, showed the molecular ion peaks at the appropriate *m*/*z* values. The ^{1}H and ^{13}C NMR spectroscopic data, and IR spectra, are in agreement with the proposed structures. The ^{1}H NMR spectrum of **3a** in $CDCl_3$ showed three sharp singlets for the methyl protons. The ^{13}C NMR spectrum of **3a** exhibited seven signals in agreement with the proposed structure. The ^{1}H NMR and ^{13}C NMR spectra of **3b**–**3i** are similar to those for **3a** except for the substituents, which showed characteristic resonances in appropriate regions of the spectrum. After reaction of 4-chlorobenzylamine, CS_2, and ethyl 3-chloroacetoacetate at room temperature intermediate **6i** was isolated and characterized.

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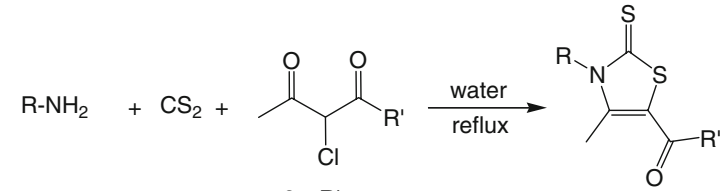
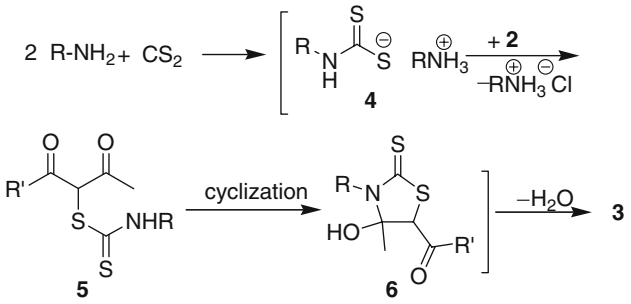
Scheme 1



1	R
a	Me
b	*n*-Bu
c	4-Cl-Bn
d	4-Me-Bn
e	4-MeO-Bn
f	2-Cl-Bn
g	1-Naphthyl-CH_2
h	Ph

2	R'
a	Me
b	OEt

3	R	R'	Yield (%)
a	Me	Me	80
b	*n*-Bu	Me	85
c	4-Cl-Bn	Me	78
d	4-Me-Bn	Me	82
e	4-MeO-Bn	Me	75
f	2-Cl-Bn	Me	68
g	1-Naphthyl-CH_2	Me	85
h	Ph	Me	65
i	4-Cl-Bn	OEt	85



Scheme 2

Mechanistically, the reaction starts with formation of an alkylammonium dithiocarbamate salt **4**, followed by addition to 2-chloro-1,3-dicarbonyl compounds to generate the acyclic dithiocarbamate derivatives **5**. Subsequent cyclization yields 4-hydroxythiazoline-2-thiones **6**. Elimination of water from **6** in the presence of alkylammonium chloride leads to *N*-alkylthiazoline-2-thiones **3** (Scheme 2).

In conclusion, we have described a convenient route to *N*-alkylthiazoline-2-thiones **3** by reaction of primary amines, CS_2, and 2-chloro-1,3-dicarbonyl compounds. This catalyst-free and green procedure may be regarded as an alternative method for preparation of *N*-alkylthiazoline-2-thiones.

Experimental

All purchased solvents and chemicals were of analytical grade and used without further purification. Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-500 Avance instrument using $CDCl_3$ as solvent and TMS as internal standard at 500 and 125.7 MHz, respectively. The mass spectra were recorded on an HP (Agilent Technology) GCMSQP5050A. Elemental analyses for C, H, N were performed using a Heraeus CHN-O-Rapid analyzer, and the results agreed favorably with calculated values.

General procedure for the synthesis of N-alkylthiazoline-2-thiones 3

To amine **1** (4 mmol) and 0.92 g CS_2 (12 mmol) in 7 cm^3 water was slowly added 2-chloro-1,3-dicarbonyl compound **2** (2 mmol). The reaction mixture was stirred for 2 h at rt and heated under reflux for 4–5 h. Addition of 4 cm^3 saturated $NaHCO_3$ solution caused an oil to separate, which in some cases solidified on standing overnight. The residue was recrystallized from *n*-hexane–toluene mixtures.

1-(2,3-Dihydro-3,4-dimethyl-2-thioxothiazol-5-yl)-1-ethanone (**3a**, $C_7H_9NOS_2$)

Pale brown oil; yield 0.30 g (80%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 2.67 (s, CH_3), 4.19 (s, CH_3) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.4$ (CH_3), 29.9 (CH_3), 41.0 (CH_3N), 121.2 (C), 146.9 (C), 187.3 (C), 188.2 (C) ppm; IR (KBr): $\bar{\nu} = 1{,}669$ (C=O), 1,648, 1,550, 1,460, 1,430, 1,361, 1,303, 1,279, 1,210, 1,140, 1,123, 990 cm^{-1}; EI-MS: *m/z* (%) 187 (M^+, 10), 158 (45), 154 (100), 71 (16), 29 (40).

1-(3-Butyl-2,3-dihydro-4-methyl-2-thioxothiazol-5-yl)-1-ethanone (**3b**, $C_{10}H_{15}NOS_2$)

Pale yellow oil; yield 0.39 g (85%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.90$ (t, $^3J = 7.5$ Hz, CH_3), 1.35 (m, CH_2), 1.61 (m, CH_2), 2.27 (s, CH_3), 2.60 (s, CH_3), 4.12 (t, $^3J = 7.5$ Hz, CH_2N) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.3$ (CH_3), 14.4 (CH_3), 19.7 (CH_2), 29.1 (CH_2), 29.9 (CH_3), 47.0 (CH_2N), 120.0 (C), 146.5 (C), 187.1 (C), 187.7 (C) ppm; IR (KBr): $\bar{\nu} = 1{,}663$ (C=O), 1,640, 1,549, 1,448, 1,417, 1,355, 1,300, 1,274, 1,197, 1,157, 1,121, 1,030, 974 cm^{-1}; EI-MS: *m/z* (%) = 229 (M^+, 15), 196 (60), 158 (55), 71 (16), 43 (100).

1-[3-[(4-Chlorophenyl)methyl]-2,3-dihydro-4-methyl-2-thioxothiazol-5-yl]-1-ethanone (**3c**, $C_{13}H_{12}ClNOS_2$)
Pale yellow crystals; yield 0.46 g (78%); m.p.: 119–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.36$ (s, CH_3), 2.52 (s, CH_3), 5.51 (s, CH_2N), 7.13 (d, $^3J = 8.3$ Hz, 2 CH), 7.29 (d, $^3J = 8.3$ Hz, 2 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 15.0$ (CH_3), 30.3 (CH_3), 49.7 (CH_2N), 120.5 (C), 128.1 (2 CH), 129.3 (2 CH), 132.6 (C), 134.1 (C), 146.9 (C), 188.0 (C), 188.7 (C) ppm; IR (KBr): $\bar{\nu} = 1{,}665$ (C=O), 1,639, 1,552, 1,481, 1,418, 1,354, 1,297, 1,295, 1,200, 1,157, 1,087, 982, 792 cm^{-1}; EI-MS: *m/z* (%) = 298 (M^+, 15), 265 (42), 158 (20), 140 (10), 126 (100).

1-[2,3-Dihydro-4-methyl-3-[(4-methylphenyl)methyl]-2-thioxothiazol-5-yl]-1-ethanone (**3d**, $C_{14}H_{15}NOS_2$)
Pale yellow crystals; yield 0.45 g (82%); m.p.: 129–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.30$ (s, CH_3), 2.42 (s, CH_3), 2.59 (s, CH_3), 5.63 (s, CH_2N), 7.17–7.22 (m, 4 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 15.3$ (CH_3), 21.0 (CH_3), 30.4 (CH_3), 50.6 (CH_2N), 122.0 (C), 127.5 (2 CH), 130.3 (2 CH), 132.9 (C), 138.3 (C), 148.0 (C), 188.6 (C), 189.9 (C) ppm; IR (KBr): $\bar{\nu} = 1{,}651$ (C=O), 1,640, 1,542, 1,506, 1,419, 1,368, 1,362, 1,295, 1,290, 1,178, 1,168, 802, 744 cm^{-1}; EI-MS: *m/z* (%) = 277 (M^+, 10), 244 (35), 158 (10), 140 (25), 105 (100).

1-[2,3-Dihydro-3-[(4-methoxyphenyl)methyl]-4-methyl-2-thioxothiazol-5-yl]-1-ethanone (**3e**, $C_{14}H_{15}NO_2S_2$)
Yellow crystals; yield 0.44 g (75%); m.p.: 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.33$ (s, CH_3), 2.52 (s, CH_3), 3.75 (s, CH_3O), 5.47 (s, CH_2N), 6.82 (d, $^3J = 8.6$ Hz, 2 CH), 7.14 (d, $^3J = 8.6$ Hz, 2 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.8$ (CH_3), 30.1 (CH_3), 49.7 (CH_2N), 55.1 (CH_3O), 114.2 (2 CH), 120.2 (C), 125.9 (C), 127.9 (2 CH), 147.1 (C), 159.2 (C–O), 187.8 (C), 188.4 (C) ppm; IR (KBr): $\bar{\nu} = 1{,}664$ (C=O), 1,638, 1,551, 1,503, 1,432, 1,350, 1,295, 1,244, 1,177, 1,155, 1,025, 806 cm^{-1}; EI-MS: *m/z* (%) = 293 (M^+, 7), 260 (30), 158 (10), 156 (20), 121 (100).

1-[3-[(2-Chlorophenyl)methyl]-2,3-dihydro-4-methyl-2-thioxothiazol-5-yl]-1-ethanone (**3f**, $C_{13}H_{12}ClNOS_2$)
Pale yellow crystals; yield 0.41 g (68%); m.p.: 114–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 2.51 (s, CH_3), 5.65 (s, CH_2N), 7.17–7.40 (m, 3 CH), 7.45 (d, $^3J = 8.5$ Hz, CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.6$ (CH_3), 30.2 (CH_3), 47.7 (CH_2N), 120.3 (C), 126.4 (CH), 126.7 (CH), 129.2 (CH), 129.4 (CH), 131.3 (C), 132.3 (C), 146.9 (C), 186.0 (C), 188.7 (C) ppm; IR (KBr): $\bar{\nu} = 1{,}660$ (C=O), 1,640, 1,550, 1,481, 1,424, 1,350, 1,291, 1,285, 1,200, 1,143, 1,079, 980, 790 cm^{-1}; EI-MS: *m/z* (%) = 298 (M^+, 20), 265 (35), 158 (20), 140 (15), 126 (100).

1-[2,3-Dihydro-4-methyl-3-(1-naphthylmethyl)-2-thioxothiazol-5-yl]-1-ethanone (**3g**, $C_{17}H_{15}NOS_2$)
Pale yellow crystals; yield 0.53 g (85%); m.p.: 202–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.48$ (s, CH_3), 2.60 (s, CH_3), 6.14 (s, CH_2N), 6.81 (d, $^3J = 7.0$ Hz, CH), 7.43 (t, $^3J = 8.0$ Hz, CH), 7.61 (t, $^3J = 7.0$ Hz, CH), 7.67 (t, $^3J = 7.0$ Hz, CH), 7.90 (d, $^3J = 8.0$ Hz, CH), 8.00 (d, $^3J = 8.0$ Hz, CH), 8.19 (d, $^3J = 8.0$ Hz, CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 15.1$ (CH_3), 30.2 (CH_3), 48.9 (CH_2N), 122.2 (C), 122.6 (CH), 123.4 (CH), 126.3 (CH), 127.1 (CH), 127.5 (CH), 128.9 (CH), 129.8 (CH), 130.7 (C), 131.3 (C), 134.8 (C), 148.1 (C), 188.2 (C), 189.5 (C) ppm; IR (KBr): $\bar{\nu} = 1{,}638$ (C=O), 1,561, 1,499, 1,418, 1,378, 1,352, 1,298, 1,285, 1,199, 1,157, 1,045, 1,020, 989, 911, 783 cm^{-1}; EI-MS: *m/z* (%) = 313 (M^+, 30), 280 (25), 158 (35), 155 (25), 141 (100).

1-(2,3-Dihydro-4-methyl-3-phenyl-2-thioxothiazol-5-yl)-1-ethanone (**3h**, $C_{12}H_{11}NOS_2$)
Yellow crystals; yield 0.32 g (65%); m.p.: 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.32$ (s, CH_3), 2.45 (s, CH_3), 7.34–7.44 (m, 2 CH), 7.54–7.66 (m, 3 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 16.5$ (CH_3), 30.9 (CH_3), 123.0 (C), 129.5 (2 CH), 130.6 (CH), 130.8 (2 CH), 138.8 (C–N), 148.0 (C), 188.6 (C), 190.6 (C) ppm; IR (KBr): $\bar{\nu} = 16{,}705$ (C=O), 1,650, 1,555, 1,510, 1,444, 1,348, 1,294, 1,249, 1,160, 810 cm^{-1}; EI-MS: *m/z* (%) = 249 (M^+, 22), 216 (28), 158 (18), 64 (22), 42 (100).

Ethyl 3-[(4-chlorophenyl)methyl]-2,3-dihydro-4-methyl-2-thioxothiazol-5-carboxylate (**3i**, $C_{14}H_{14}ClNO_2S_2$)
Pale yellow crystals; yield 0.56 g (85%); m.p.: 64–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.32$ (t, $^3J = 7.1$ Hz, CH_3), 2.53 (s, CH_3), 4.29 (q, $^3J = 7.1$ Hz, CH_2O), 5.50 (s, CH_2N), 7.14 (d, $^3J = 7.3$ Hz, 2 CH), 7.28 (d, $^3J = 7.3$ Hz, 2 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 14.3 (CH_3), 49.6 (CH_2N), 61.6 (CH_2O), 128.0 (CH), 128.6 (C), 129.1 (CH), 132.7 (C), 133.9 (C), 147.9 (C), 159.8 (C=O), 189.7 (C=S) ppm; IR (KBr): $\bar{\nu} = 1{,}690$ (C=O), 1,641, 1,562, 1,474, 1,400, 1,350, 1,293, 1,230, 1,210, 1,137, 1,080, 972, 785 cm^{-1}; EI-MS: *m/z* (%) = 328 (M^+, 10), 295 (31), 283 (40), 188 (15), 140 (12), 126 (100).

Ethyl 3-[(4-chlorophenyl)methyl]-4-hydroxy-4-methyl-2-thioxothiazolidine-5-carboxylate (**6i**, $C_{14}H_{16}ClNO_3S_2$)
Colorless crystals; yield 0.66 g (95%); m.p.: 224–230 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.29$ (t, $^3J = 7.1$ Hz, CH_3), 1.59 (s, CH_3), 4.06 (s, CH), 4.25 (q, $^3J = 7.1$ Hz, CH_2O), 4.84 (d, $^2J = 15.2$ Hz, CH), 5.10 (d, $^2J = 15.2$ Hz, CH), 5.19 (s, OH), 7.28 (d, $^3J = 8.3$ Hz, 2 CH), 7.34 (d, $^3J = 8.3$ Hz, 2 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.9$ (CH_3), 24.4 (CH_3), 47.5 (CH_2N), 51.8 (CH), 63.0 (CH_2), 97.9 (C), 128.7 (2 CH), 129.0 (2 CH), 133.3 (C), 135.0 (C), 169.9

(C=O), 191.6 (C=S) ppm; IR (KBr): $\bar{\nu}$ = 3,410 (OH), 1,705 (C=O), 1,561, 1,499, 1,418, 1,378, 1,352, 1,298, 1,285, 1,199, 1,157, 1,045, 1,020, 989, 911, 783 cm^{-1}; EI-MS: *m/z* (%) = 346 (M^+, 5), 328 (20), 295 (15), 283 (31), 188 (8), 140 (20), 126 (100).

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