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Solvent-free synthesis of 1-[3-alkyl-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanones in a multicomponent reaction

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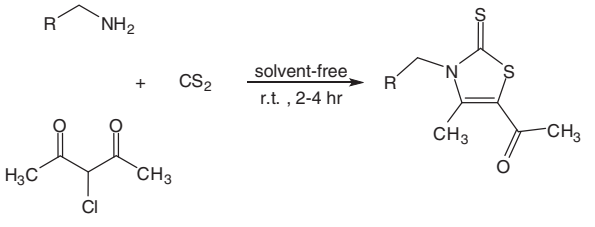
A simple and efficient one-pot synthesis of 1-[3-alkyl-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanones from the reaction of primary alkylamines and carbon disulfide in the presence of 3-chloro acetylacetone is described. This protocol has several advantages such as lack of need for a solvent and catalyst, high yields, mild conditions and short reaction times.



Keywords: 3-chloro acetylacetone; 2-thioxo-2,3-dihydrothiazole; carbon disulfide; primary alkylamines; multicomponent reaction

1. Introduction

Thiazoles and their derivatives exhibit various biological activities such as antimicrobial, anti-inflammatory, antiviral, antituberculosis and cytotoxic activities (*1–6*). For example, the thiazolium ring present in vitamin B_1 serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto-acids (*7*). Especially noteworthy is the observation that some thiazolines show interesting anti-HIV or anticancer activities and can inhibit cell division

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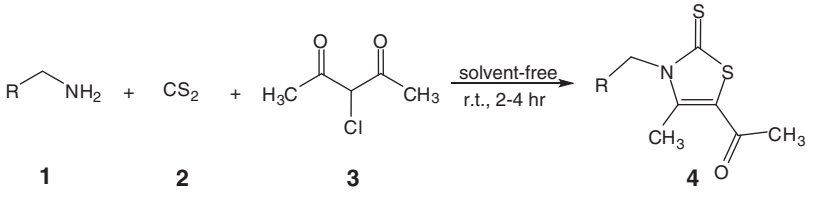
(*8–10*). In view of the importance of thiazoles and their derivatives, several methods for their syntheses have been developed. The most widely used method is Hantzsch synthesis involving the reaction of α-halocarbonyl compounds with thioureas or thioamides (*11–13*). Recently, syntheses of thiazol-2-imine derivatives from benzoyl phenylthioureas and *in situ* generated α-bromoketones obtained by the reaction of enolizable ketones with 1,10-(ethane-1,2-diyl)dipyridinium bistribromide have been reported (*14*, *15*). Thiazole derivatives were also synthesized by using catalysts such as ammonium 12-molybdo phosphate (*16*), cyclodextrin (*17*), iodine (*18a*), and silica chloride (*18b*) in organic solvents such as 1-methyl-2-pyrrolidinone (*19*) and with the use of microwave irradiation (*20*). However, in spite of their potential utility, many of these methods suffer from drawbacks, such as harsh reaction conditions, cumbersome product isolation procedures, and expensive catalysts.

As a part of our current studies, on the synthesis of sulfur-containing organic compounds (*21*, *22*), in this article, we describe an efficient method for the synthesis of functionalized 2,3-dihydrothiazoles under solvent-free conditions. This catalyst-free and one-pot synthetic method is facile with an easy workup procedure that gives pure target compounds containing several potential centers for further modification.

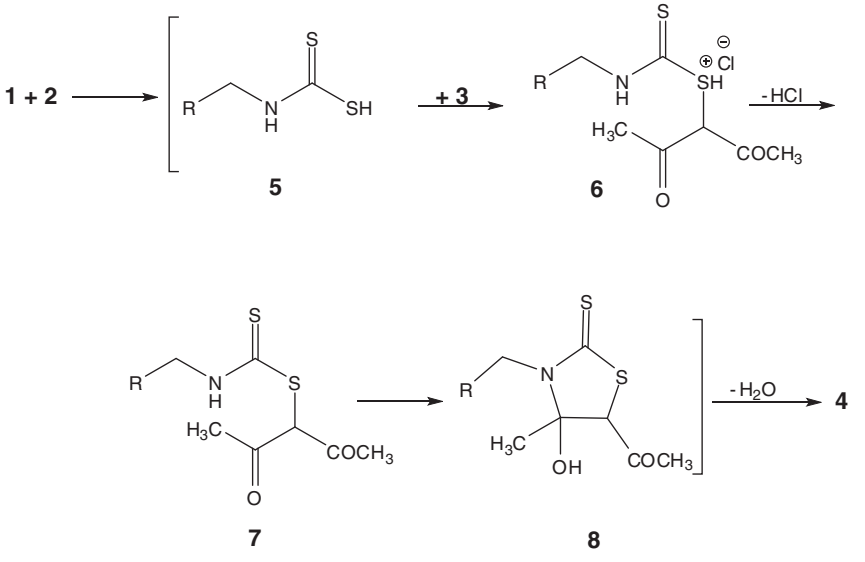
2. Results and discussion

The reactions of alkylamines **1** and carbon disulfide **2** in the presence of 3-chloro acetylacetone **3** proceed smoothly at room temperature to produce 1-[3-alkyl-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanones **4a**–**4j** in good yields after purification (Scheme 1). In this procedure, we report a simple method for thiazole synthesis via the reaction of alkyldithiocarbamic acids (**5**; Scheme 2) with 3-chloro acetylacetone. The alkyl-dithiocarbamic acid



1, 4	R	Yield(%)
a	4-MeO-C_6H_4	82
b	4-Cl-C_6H_4	90
c	2-Cl-C_6H_4	88
d	4-Me-C_6H_4	97
e	2-MeO-C_6H_4	96
f	C_6H_5	94
g	4-F-C_6H_4	85
h	Me	84
i	Et	93
j	^{n}Pr	86

Scheme 1. The three-component one-pot synthesis of 2,3-dihydrothiazoles **4**.



Scheme 2. Plausible mechanism for the formation of 2,3-dihydrothiazoles **4**.

derivatives were prepared from the reaction of **1** and **2**. Functionalized 2,3-dihydro thiazoles **4** were obtained from the reaction of these dithiocarbamic acids with **3**.

The structures of compounds **4a**–**4j** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectral data. The ^{1}H NMR spectrum of **4e** in $CDCl_3$ showed seven signals for methyl ($\delta = 2.39$ and 2.51 ppm), methoxy ($\delta = 3.90$ ppm), and methylene ($\delta = 5.56$ ppm) protons along with signals ($\delta = 6.78$, 6.86–6.92, and 7.29 ppm) for the aromatic protons. The ^{13}C NMR spectrum of **4e** showed 14 signals including methyl ($\delta = 15.3$ and 22.7 ppm), methylene ($\delta =$ 45.3 ppm), and methoxy ($\delta = 55.4$ ppm) carbons along with signals ($\delta = 110.46$–147.6 ppm) for the two olefinic and six aromatic carbons that are in agreement with the proposed structure. In addition, ^{13}C NMR peaks in the spectrum of **4e** at 188.2 and 188.68 ppm are diagnostic for α, β-carbonyl and thiocarbonyl groups, respectively. Partial assignments of these resonances are given in Section 4.

A plausible mechanism for this reaction is given in Scheme 2 and is initiated by reaction of the primary alkylamine and carbon disulfide to give the dithiocarbamic acid derivatives **5**. Subsequent nucleophilic alkylation of **5** with 3-chloro acetylacetone **3** yields intermediate **6**. This intermediate undergoes HCl elimination and subsequent intramolecular cyclization to form the heterocyclic intermediate **8**, which generates **4** by elimination of water (Scheme 2).

3. Conclusions

We have reported a convenient transformation involving carbon disulfide and primary alkyl amines in the presence of 3-chloro acetylacetone, which affords 1-[3-alkyl-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanones. This new protocol has several advantages such as the lack of need for a solvent and catalyst, high yields, short reaction times, simple experimental workup procedure, and neutral reaction conditions performed at room temperature by simple mixing of the starting materials. The procedure described here also provides an efficient one-pot methodology for the preparation of functionalized 2,3-dihydrothiazoles.

4. Experimental

4.1. *General*

Amines, carbon disulfide, and 3-chloro acetylacetone were obtained from Fluka and were used without further purification; IR spectra: Shimadzu IR-460 spectrometer with a KBr liquid cell; ^{1}H and ^{13}C NMR spectra: Bruker DRX-400 AVANC instrument; in $CDCl_3$ at 400.13 and 100.61 MHz, respectively, δ in ppm, and J in Hz; Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer. The analyses data were in agreement with the proposed structures.

4.2. *General procedure for the preparation of compounds 4a–4j*

A mixture of 0.175 g of carbon disulfide (2.3 mmol) and the primary alkylamine **1** (2 mmol) was stirred at room temperature for 30 min. Then, 3-chloro acetylacetone (2 mmol) was added to the reaction mixture and stirred at room temperature. After completion of the reaction [2–4 h; TLC (*n*-hexane/AcOEt 3:1)], the reaction mixture was purified by column chromatography [silica gel (230–240 mesh; Merck), *n*-hexane/AcOEt 4:1)] to afford the pure title compounds.

4.2.1. *1-[3-(4-Methoxybenzyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4a**)*

Yellow oil; yield: 0.24 g (82%). IR (KBr liquid cell): 3050 (CH arom), 2910 (CH aliph), 1670 (C9O), 1510 (C9C), 1160 (C9S) cm^{-1}. ^{1}H NMR: δ 2.38 (3H, s, CH_3), 2.57 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 5.52 (2H, s, CH_2), 6.87 (2H, d, $^{3}J_{HH} = 8.4$ Hz, 2 CH), 7.18 (2H, d, $^{3}J_{HH} = 8.4$ Hz, 2 CH) ppm.^{13}C NMR: δ 15.3 (CH_3), 25.6 (CH_3), 49.9 (CH_2), 55.3 (OCH_3), 111.8 (C), 114.3 (2 CH), 126.3(C), 128.1 (2 CH), 140.4 (C), 159.3 (C), 187.6 (C9O), 189.7 (C9S) ppm. Anal. Calcd for $C_{14}H_{15}NO_2S_2$ (293.4): C, 57.31; H, 5.15; N, 4.77. Found: C, 57.2; H 5.26; N, 4.8%.

4.2.2. *1-[3-(4-Chlorobenzyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4b**)*

Yellow oil; Yield: 0.26 g (90%). IR (KBr liquid cell): 3100(CH arom), 2900 (CH aliph), 1680 (C9O), 1565 (C9C), 1170 (C9S) cm^{-1}. ^{1}H NMR: δ 2.45 (3H, s, CH_3), 2.61 (3H, s, CH_3), 5.23 (2H, s, CH_2), 7.32 (2H, d, $^{3}J_{HH} = 8.3$ Hz, 2 CH), 7.38(2H, d, $^{3}J_{HH} = 8.2$ Hz, 2 CH) ppm. ^{13}C NMR: δ 15.6 (CH_3), 28.4 (CH_3), 47.78 (CH_2), 99.8 (C), 128.1 (2 CH), 129.3 (2 CH), 132.5 (C), 134.6 (C), 161.2 (C), 188.4 (C9O), 189.5 (C9S) ppm. Anal. Calcd for $C_{13}H_{12}ClNOS_2$ (291.83): C, 51.44; H, 4.15; N, 4.8. Found: C, 51.2; H 4.1; N, 4.73%.

4.2.3. *1-[3-(2-Chlorobenzyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4c**)*

Yellow oil; Yield: 0.27 g (88%). IR (KBr liquid cell): 3050 (CH arom), 2810 (CH aliph), 1675 (C9O), 1590 (C9C), 1165 (C9S) cm^{-1}. ^{1}H NMR: δ 2.41 (3H, s, CH_3), 2.51 (3H, s, CH_3), 5.66 (2H, s, CH_2), 6.80(1H, d,$^{3}J_{HH} = 7.6$ Hz, CH), 7.20–7.29 (2H, m, 2 CH), 7.44 (1H, d,$^{3}J_{HH} = 7.6$ Hz, CH) ppm. ^{13}C NMR: δ 14.7 (CH_3), 30.4 (CH_3), 47.7 (CH_2), 112.1 (C), 126.5 (CH), 127.5 (CH), 129.2 (CH), 129.8 (CH), 131.4 (C), 132.3 (C), 148 (C), 188.18 (C9O), 188.73 (C9S) ppm. Anal. Calcd for $C_{13}H_{12}ClNOS_2$ (291.83): C, 51.44; H, 4.15; N, 4.8. Found: C, 51.2; H 4.1; N, 4.73%.

4.2.4. *1-[3-(4-Methylbenzyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4d**)*

Yellow oil; Yield: 0.27 g (97%). IR (KBr liquid cell): 3000 (CH arom), 2800 (CH aliph), 1660 (C9O), 1550 (C9C), 1158 (C9S) cm^{-1}. ^1H NMR: δ 2.33 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.55 (3H, s, CH_3), 5.53 (2H, s, CH_2), 7.09 (2H, d, $^3J_{HH} = 7.6$ Hz, 2 CH), 7.15 (2H, d, $^3J_{HH} = 8$ Hz, 2 CH) ppm. ^{13}C NMR: δ 15.03 (CH_3), 21.13 (CH_3), 30.36 (CH_3), 50.2 (CH_2), 120.18 (C), 126.56 (2 CH), 129.72 (2 CH), 131 (C), 137.97 (C), 148.43 (C), 188.2 (C9O), 188.67 (C9S) ppm. Anal. Calcd for $C_{14}H_{15}NOS_2$ (277.4): C, 60.61; H, 8.52; N, 5.05. Found: C, 60.6; H 8.48; N, 5.1%.

4.2.5. *1-[3-(2-Methoxybenzyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4e**)*

Yellow oil, Yield: 0.28 g (96%). IR (KBr liquid cell): 3050 (CH arom), 2900 (CH aliph), 1670 (C9O), 1558 (C9C),1160 (C9S) cm^{-1}. ^1H NMR: δ 2.39 (3H, s, CH_3), 2.51 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 5.56 (2H, s, CH_2), 6.78 (1H, d, $^3J_{HH} = 7.2$ Hz, CH), 6.86–6.93 (2H, m, 2 CH), 7.28 (1H, d, $^3J_{HH} = 8.8$ Hz, CH) ppm. ^{13}C NMR: δ 15.3 (CH_3), 22.7 (CH_3), 45.3 (CH_2), 55.4 (OCH_3), 110.46 (C), 120.19 (CH), 120.9 (2CH), 121.9 (CH), 126.2 (C), 129.1 (C), 147.6(C), 188.21 (C9O), 188.68 (C9S) ppm. Anal. Calcd for $C_{14}H_{15}NO_2S_2$ (293.4): C, 57.31; H, 5.15; N, 4.77. Found: C, 57.2; H 5.26; N, 4.8%.

4.2.6. *1-[3-Benzyl-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4f**)*

Yellow oil; yield: 0.25 g (94%). IR (KBr liquid cell): 3020 (CH arom), 2920 (CH aliph), 1670 (C9O), 1558 (C9C), 1180 (C9S) cm^{-1}. ^1H NMR: δ 2.39 (3H, s, CH_3), 2.55 (3H, s, CH_3), 5.58 (2H, s, CH_2), 7.2 (2H, d, $^3J_{HH} = 6.8$ Hz, 2 CH), 7.33–7.36 (3H, m, 3 CH) ppm. ^{13}C NMR: δ 15 (CH_3), 22.7 (CH_3), 50.37 (CH_2), 124.5 (C), 126.6 (CH), 128.2 (2CH), 129.1 (2CH), 134 (C), 147.4 (C), 188.21 (C9O), 188.72 (C9S) ppm. Anal. Calcd for $C_{13}H_{13}NOS_2$ (263.4): C, 59.27; H, 4.97; N, 5.32. Found: C, 59.3; H 4.88; N, 5.3%.

4.2.7. *1-[3-(4-Fluorobenzyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4g**)*

Yellow oil; yield: 0.24 g (85%). IR (KBr liquid cell): 3050 (CH arom), 2910 (CH aliph), 1670 (C9O), 1559 (C9C), 1160 (C9S) cm^{-1}. ^1H NMR: δ 2.37 (3H, s, CH_3), 2.55 (3H, s, CH_3), 5.53 (2H, s, CH_2), 7.03–7.34 (4H, m, 4 CH) ppm. ^{13}C NMR: δ 14.99 (CH_3), 29.7 (CH_3), 49.67 (CH_2), 100.1 (C), 128.6 (2 CH), 129.9 (2 CH), 147.4 (C), 150.9 (C), 161.9 (C-F, $^1J_{CF} = 264.7$ Hz), 188.5 (C9O), 189.7 (C9S) ppm. Anal. Calcd for $C_{13}H_{12}FNOS_2$ (281.4): C, 55.48; H, 4.29; N, 4.99. Found: C, 55.5; H 4.3; N, 5%.

4.2.8. *1-[3-Ethyl-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4h**)*

Colorless oil; yield: 0.17 g (84%). IR (KBr liquid cell): 3048 (CH arom), 2910–2980 (CH aliph), 1668 (C9O), 1558 (C9C), 1160 (C9S) cm^{-1}. ^1H NMR: δ 1.34 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 2.36 (3H, s, CH_3), 2.69 (3H, s, CH_3),4.31 (2H, q, $^3J_{HH} = 6.8$ Hz, CH_2) ppm. ^{13}C NMR: δ 12.6 (CH_3), 14.1 (CH_3), 22.69 (CH_3), 42.56 (CH_2), 120.19 (C), 146.68 (C), 187.22 (C9O), 188.19 (C9S) ppm. Anal. Calcd for $C_8H_{11}NOS_2$ (201.31): C, 53.69; H, 5.51; N, 6.96. Found: C, 53.7; H 5.5; N, 6.95%.

4.2.9. *1-[3-(^{n}Propyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4i**)*

Colorless oil; yield: 0.2 g (93%). IR (KBr liquid cell): 3040 (CH arom), 2950 (CH aliph), 1665 (C9O), 1550 (C9C), 1165 (C9S) cm^{-1}. ^1H NMR: δ 1.02 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.81 (2H, six, $^3J_{HH} = 7.1$ Hz, CH_2), 2.37 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.21 (2H, q, $^3J_{HH} = 7.2$ Hz, CH_2) ppm. ^{13}C NMR: δ 11.18 (CH_3), 14.1 (CH_3), 14.2 (CH_2), 22.7 (CH_3), 48.86 (CH_2), 121.8 (C), 147.8 (C), 187.51 (C9O), 188.27 (C9S) ppm. Anal. Calcd for $C_9H_{13}NOS_2$ (215.33): C, 50.19; H, 6.08; N, 6.5. Found: C, 50.2; H 6.1; N, 6.51%.

4.2.10. *1-[3-(^{n}Butyl)-4-methyl-2-thioxo-2,3-dihydrothiazole-5-yl]-ethanone (**4j**)*

Colorless oil; yield: 0.2 g (86%). IR (KBr liquid cell): 3050 (CH arom), 2960 (CH aliph), 1668 (C9O), 1556 (C9C), 1160 (C9S) cm^{-1}. ^1H NMR: δ 0.88 (3H, t, $^3J_{HH} = 6.8$ Hz, CH_3), .99 (3H, t, $^3J_{HH} = 7.6$ Hz, CH_3), 1.43 (2H, six, $^3J_{HH} = 7.6$ Hz, CH_2), 1.72 (2H, qui, $^3J_{HH} = 6.8$ Hz, CH_2), 2.37 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.22 (2H, t, $^3J_{HH} = 7.6$ Hz, CH_2) ppm. ^{13}C NMR: δ 14.68 (CH_3), 14.71 (CH_3), 14.8 (CH_2), 20.09 (CH_3), 22.7 (CH_2), 47.3 (CH_2), 120.07 (C), 146.88 (C), 187.41 (C9O), 188.24 (C9S) ppm. Anal. Calcd for $C_{10}H_{15}NOS_2$ (229.4): C, 52.35; H, 6.59; N, 6.1. Found: C, 52.4; H 6.61; N, 6.12%.

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