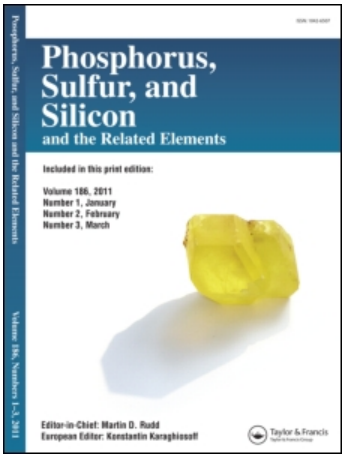

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N,N′-dimethylthiourea reacts with dialkyl acetylenedicarboxylates in acetone to form 1:1 adducts, which undergo a cyclization reaction to produce alkyl (Z)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden] acetates, in fairly good yields. The reaction is completely stereoselective. The toxicity effects of the products against protozoan (Euplots) in the culture were investigated.

Keywords 1,3-thiazolan; acetylenic ester; biological activity; Michael addition; N,N′-dimethylthiourea; protozoan; stereoselectivity

INTRODUCTION

Thiazole derivatives are important compounds due to their broad range of biological activities. They have attracted a great deal of interest due to their antibacterial, antifungal, anti-inflammatory, and antiviral activities.[1] They are also useful as anti-allergic, anthelmintic agents and as sedative hypnotics.[1] In addition to being used in the pharmaceutical industry,[1–3] they also find a wide application in the dye and photographic industry.[1] There are various methods for the synthesis of thiazole derivatives.[4,5] Development of simple synthetic routes for widely-used organic compounds from readily available reagents is

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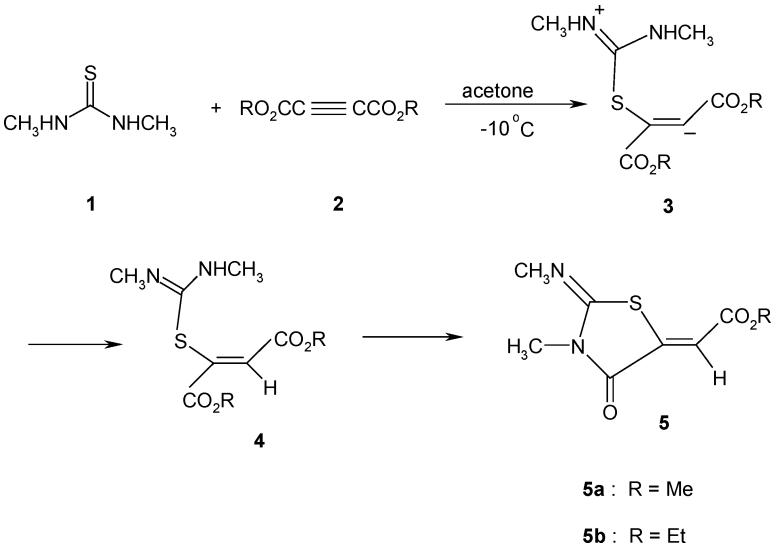
one of the major tasks in organic chemistry.[6] Owing to these characteristics and our interest in the synthesis of heterocycles,[7–10] we were prompted to synthesize alkyl (*Z*)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden] acetates (**5**) from dialkyl acetylenedicarboxylates (**2**) and N, N′-dimethylthiourea (**1**) in acetone in fairly good yields (Scheme 1).



SCHEME 1

RESULTS AND DISCUSSION

The reaction of N,N′-dimethylthiourea **1** with acetylenic esters **2** proceeded at −10°C in acetone within 15 min and alkyl (*Z*)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden] acetates **5** was synthesized. A plausible mechanism for the formation of **5** is indicated in Scheme 1. Compounds **5** may result from initial Michael addition reaction of N,N′-dimethylthiourea **1** to the acetylenic esters **2** and intramolecular proton transfer in the 1:1 adduct **3**, followed by attack of the imine nitrogen on the carbonyl group of the ester to form products **5**, in acetone in fairly good yields (Scheme 1). TLC indicated that the reaction was completed after 15 min. The reaction proceeds smoothly and cleanly under the reaction conditions. The structures of **5a–b** were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. The reaction is completely stereoselective. Partial assignments of the ^{1}H NMR and ^{13}C NMR resonances are given in the Experimental section. The presented

TABLE I The Toxicity Effects of 5a and 5b on Protozoan (Euplots) in the Culture (Mean ± SD)

Chemicals	Concentration (mg/ml)	(Die/live)*100 ± SD
5a	8	0
	10	0
	12	10 ± 5.6
	18	22 ± 8.4
	22	35 ± 7.3
	27	52 ± 8.2
	30	68 ± 7.3
	35	85 ± 5.6
	39	93 ± 6.3
	45	100
	50	100
5b	7	0
	8	0
	9.6	14 ± 5.2
	12	27 ± 7.8
	14	51 ± 6.7
	15.5	75 ± 7.5
	22	88 ± 5.4
	23	95 ± 4.2
	24	100
	26	100

method is an efficient and one-pot stereoselective method for preparing alkyl (*Z*)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden] acetates.

BIOLOGICAL ACTIVITY

The synthesized compounds were tested for antiprotozoan activity against various protozoans such as Euplots. The new compounds have manifested significant anti-protozoan activity that is presented in Table I for **5a** and **5b**. We found that the new synthesized materials were sensed by protozoan. The chemotaxis activities of protozoan are shown in Table II for **5a** and **5b**. The protozoans have manifested significant negative chemotaxis activities against **5a** and **5b**. We used distilled water as a control group. The protozoans have not manifested any chemotaxis activities against distilled water (Table II).

Antiprotozoan Test

The protozoan cells including Amoeba, Paramecium, Vorticella, Eupletes, and Euglena were cultivated on plant infusion media for

TABLE II The Chemotaxis Activities of Protozoan Against 5a, 5b and Distilled Water in the Culture (Mean ± SD)

Chemical	Pre-test population in culture without chemical	Post-test population in culture with chemical	Post-test population in culture without chemical	Statistical considerations
5a	75 ± 14.7	8 ± 3.5	71 ± 12.4	Significant $P < 0.001$
5b	66 ± 9.5	6 ± 2.9	46 ± 6.2	Significant $P < 0.001$
Distilled water	72 ± 8.4	29 ± 7.1	27 ± 6.7	Not significant

24 h in 25–35°C. Euplots were selected as a typical species. Euplots was cultivated for 20 h in 25–35°C in the rich organic media.[11,12] Then, the stock concentrations of **5a–b** were prepared. Therefore, anti-protozoan activities of thiazolans (**5a–b**) were tested by various concentrations of them as following: (1) The prepared culture contains various protozoans such as Euplots; (2) the 500 μl of culture solution was added into a microtube. The population of Euplots on 10 μl of this culture solution was determined in the surface of culture microtube; (3) the 50 μl of various concentrations of **5a** and **5b** was added to 50 μl of culture microtube (Table I); (4) the responses of Euplots to various concentrations of **5a–b** in the culture solution were studied after 10, 30, and 60 minutes; (5) the population of die and live Euplots in the 10 μl of culture solution were determined by light microscope; and (6) the last step was performed more and more until we obtained lethal dose (LD) between LD_0 and LD_{100}.

Chemotaxis Test

The ability of chemical detection (chemotaxis) in the protozoan is the main aim of this examination. Chemotaxis tests were performed by sublethal doses. The steps of chemotaxis studies were done as following: (1) The 10 μl of culture solution was poured on object-slide; (2) the 10 μl of sublethal concentrations of **5a** and **5b** were added to the near of 10 μl of the culture solution on object-slide; (3) A narrow thin groove was created between two drops that connected them; and (4) the population of Euplots was determined in both environments after 10 min. For comparison, distilled water was replaced as a control solution. The steps of control group were done the same as **5a** and **5b**. The population of Euplots was determined after 10 min.

CONCLUSION

In summary, we have developed a new and efficient, one-pot stereoselective method for preparing of alkyl (*Z*)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden]acetates, in fairly good yields. The compounds have manifested significant anti-protozoan activity. Other aspects of this process are under investigation.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER Spectrospin spectrometer at 250, and 62.5 MHz, respectively.

General Procedure for the Preparation of Alkyl (Z)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden]acetates (5a–b)

To a magnetically stirred solution of N, N′-dimethylthiourea **1** (0.104 g, 1 mmol) in acetone (5 ml) was added dropwise a mixture of **2** (1 mmol) in acetone (2 ml) at −10°C over 15 min. The mixture was then stirred at −10°C for 15 min. Then 2 ml of water was added and crystals of **5** were collected by filtration.

Selected Data for Methyl (Z)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden]acetate (5a)

White crystals, m.p. 157.5–159.5°C, yield 59.8%. IR (KBr) (υ_{max}, cm^{-1}): 3500; 1723; 1662. ^{1}H NMR ($CDCl_3$): 3.27 (3H, s, N—CH3), 3.29 (3H, s, =N—CH_3), 3.84 (3H, s, OCH_3); 6.88 (1H, s, =CH). ^{13}C NMR ($CDCl_3$) δ_C: 29.09 (N—CH3), 38.94 (=N—CH_3), 52.44 (OCH_3), 115.25 (=CH); 141.20 (=CS); 150.71 (C=N); 164.76 (C=O of ester) and 166.40 (C=O of ketone).

Selected Data for Ethyl (Z)-2-[3-methyl-2-(methylimino)-4-oxo-1,3-thiazolan-5-yliden]acetate (5b)

Light yellow crystals, m.p. 64.0–65.5°C, yield 56.2%. IR (KBr) (υ_{max}, cm^{-1}): 3469; 2977; 2954; 1723; 1662. ^{1}H NMR ($CDCl_3$) δ_H: 1.34 (3H, t, $^{3}J_{HH} = 7.1$ Hz, CH_3); 3.28 (3H, s, N—CH3), 3.29 (3H, s, =N—CH_3), 4.29 (2H, q, $^{3}J_{HH} = 7.1$ Hz, OCH_2); 6.89 (1H, s, =CH). ^{13}C NMR ($CDCl_3$) δ_C: 14.16 (CH_3), 29.07 (N—CH3), 38.92 (=N—CH_3), 61.61 (OCH_2), 115.78 (=CH); 140.87 (=CS); 150.88 (C=N); 164.84 (C=O of ester) and 166.00 (C=O of ketone).

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