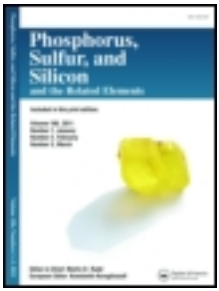

Phosphorus, Sulfur, and Silicon and the Related Elements

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One-Pot Stereoselective Synthesis of Alkyl (Z)-2-[4-Oxo-3-phenyl-2-(phenylimino)-1,3-thiazolan-5-yliden]acetates from Acetylenic Esters and N, N′-Diphenylthiourea

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One-Pot Stereoselective Synthesis of Alkyl (*Z*)-2-[4-Oxo-3-phenyl-2-(phenylimino)-1,3-thiazolan-5-yliden]acetates from Acetylenic Esters and N, N′-Diphenylthiourea

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N, N′-diphenylthiourea reacts with dialkyl acetylenedicarboxylates in acetone to form 1:1 adducts, which undergo a cyclization reaction to produce alkyl (Z)-2-[4-oxo-3-phenyl-2-(phenylimino)-1,3-thiazolan-5-yliden]acetates in fairly good yields. NMR spectra indicated that the reaction is completely stereoselective.

Keywords Acetylenic ester; Michael addition; N, N′-diphenylthiourea; stereoselectivity; 1,3-thiazolan

INTRODUCTION

For several years, acetylenic esters have been attracting the attention of organic chemists.[1–13] Acetylenic esters are reactive systems and take part in many chemical syntheses.[1–13] The compounds act almost as Michael acceptors in organic reactions.[1–13] In recent years, there has been increased interest in the applications of acetylenic esters in multicomponent synthesis.[1–13] Because of the atom economy, convergent character, and simplicity of one-pot procedures, multicomponent condensation reactions (MCRs) have an advantageous position among other reactions.[1,14] The discovery and development of novel MCRs are receiving growing interest from industrial chemistry research groups, and MCRs represent a new challenge for organic chemists and to the basic understanding of organic chemistry itself.[1,14] Owing to these characteristics and our interest in the synthesis of heterocycles,[13–16] we were prompted to synthesize alkyl (*Z*)-2-[4-oxo-3-phenyl-2-(phenylimino)-1,3-thiazolan-5-yliden]acetates (**5**) from N, N′-diphenylthiourea (**1**) and

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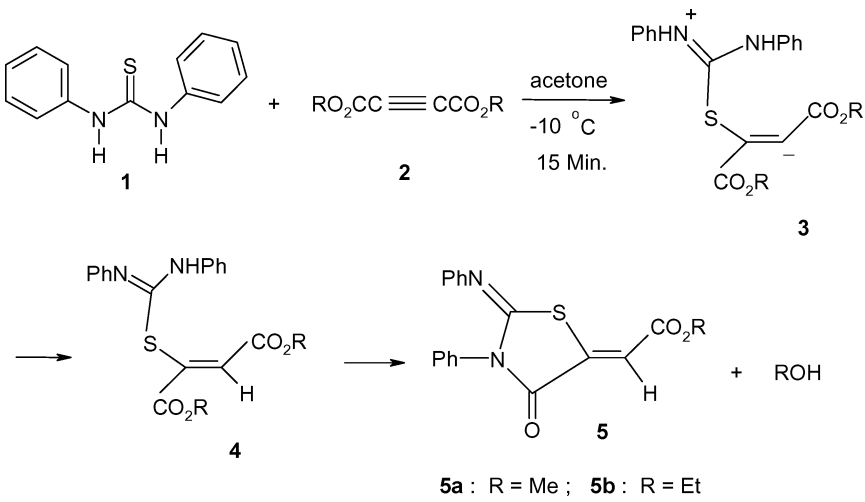

SCHEME 1

dialkyl acetylenedicarboxylates (**2**) in acetone in fairly good yields (Scheme 1).

BIOLOGICAL AND INDUSTRIAL IMPORTANCE OF THIAZOLAN DERIVATIVES

Thiazolan[17–19] skeletons are important compounds due to their broad range of biological activities.[20–34] It is well known that thiazolyl derivatives possess anti-inflammatory properties.[20–25] Today's requirements demand novel medicinal remedies possessing different degrees of selectivity and specificity depending on their purpose. The process of inflammation often becomes chronic, and the human organism needs drug therapy support in periods of acute attacks. Therefore, an increase of the variety of specific and selective anti-inflammatory remedies is an important task, especially due to its positive influence on the chronic sick rate decrease. Some anticancer drugs, such as blenoxane, bleomycine, and tiazofurin, that contain thiazolyl moiety in their structure, are known as antineoplastics.[26] In addition, several thiazolyl derivatives were found to be potent antitumor agents.[26–28] Since arachidic acid (AA) metabolism results in the generation of mutagens that damage DNA and induce mutations, members of arachidic acid enzymes, especially the lipoxygenase pathway, have been reported to play a significant role in carcinogenesis. Inhibitors of AA metabolism can reverse the production of these metabolites resulting in recruitment

of apoptotic cell clearance.[29] Thiazole derivatives have attracted a great deal of interest owing to their antibacterial, antifungal, anti-inflammatory, and antiviral activities.[30] They are also useful as anti-allergic, anthelmintic agents and as sedative hypnotics.[30] It is also well known that the thiazole moiety can be important for significant biological activity.[33,34] In addition to being used in the pharmaceutical industry,[30–32] they also find wide applications in the dye and photographic industry.[30]

RESULTS AND DISCUSSION

The compound (**5**) may result from an initial Michael addition reaction of N, N′-diphenylthiourea **1** to the acetylenic ester **2** and concomitant intramolecular protontransfer of the 1:1 adduct **3**, followed by attack of the imine nitrogen on the carbonyl group of ester to form product **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 mechanism of the reaction has not been established experimentally. However, a possible explanation is proposed in Scheme 1. The formulas of the products **5a–b** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra (See Experimental section). In this reaction, only one stereoisomer was observed, and therefore the reaction is completely stereoselective. Based on our previous reports in the areas of syntheses and structures (NMR data and single crystal X-ray structure determination)[4,13,16] of electron-poor alkenes and comparison of the structural data with the structural data of the compounds **5**, we have concluded that the stereochemistry of the compounds **5** are *Z* (for example, for the *Z* stereoisomers, =CH of alkene showed distinct resonances at $\delta = 6.90$–7.20 ppm and for *E* stereoisomers, at $\delta = 5.80$–6.60 ppm in their ^{1}H NMR spectra).[4,13,16] The IR spectrum of **5a** showed strong adsorptions at 3062 (CH, aromatic), 2954 (CH, aliphatic), 1731 (C=O, ester), 1646 (C=N, imine), 1608 (C=C), and 1192 (C-O, ester) cm^{-1} indicating the presence of mentioned groups in the formula. The ^{1}H NMR spectrum of **5a** compound exhibited four signals readily recognized as arising from one OMe groups ($\delta = 3.82$ ppm, s), CH ($\delta = 7.00$ ppm, s) and aromatic moieties ($\delta = 7.1$–7.6 ppm, m and $\delta = 6.95$ ppm, d, $^3J_{HH} = 8.0$ Hz). The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 14 distinct resonances in agreement with the **5a** formula. Partial assignment of these resonances is given in the spectral analysis section (see Experimental section). The ^{1}H and ^{13}C NMR spectra of compound **5b** are similar to those of **5a**, except for the ester group,

which exhibits characteristic signals with appropriate chemical shifts (see Spectral Analysis section).[3,4]

CONCLUSION

In summary, we have developed a new and efficient, one-pot stereoselective method for preparing of alkyl (*Z*)-2-[4-oxo-3-phenyl-2-(phenylimino)-1,3-thiazolan-5-yliden]acetates (**5**) from N, N′-diphenylthiourea (**1**) and dialkyl acetylenedicarboxylates (**2**) in acetone in fairly good yields (Scheme 1). We believe the reported method offers a simple and efficient route for the preparation of the thiazoles **5** (Scheme 1). Its ease of work-up and fairly good yields make it a useful addition to modern synthetic methodologies.[3,4] 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-[4-oxo-3-phenyl-2-(phenylimino)-1,3-thiazolan-5-yliden]acetates (5a–b)

To a magnetically stirred solution of N, N′-diphenylthiourea **1** (0.23 g, 1.0 mmol) in acetone (5 mL) was added dropwise a mixture of **2** (0.13 mL, 1.0 mmol) in acetone (2 mL) at –10°C over 15 min. The mixture was then stirred at –10°C for 15 min and then allowed to warm up to room temperature. The solvent was removed under reduced pressure, and products were recrystallized in ethanol (95%). The crystals of **5** were collected by simple filtration and dried at room temperature. The characterization data of the compounds (**5a–b**) are given below:

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

Light yellow crystals, m. p. 117.5–118.5, yield 83%. IR (KBr) (υ_{max}, cm^{-1}): 3062, 2954, 1731, 1646, 1608, 1500, 1377, 1323, 1192, 769, 700, and 585. ^{1}H NMR ($CDCl_3$) δ_H: 3.82 (3 H, s, OCH_3); 6.95 (2 H, d, $^{3}J_{HH} = 8.0$ Hz, arom.); 7.00 (1 H, s, =CH); 7.1–7.6 (8 H, m, arom.). ^{13}C NMR ($CDCl_3$) δ_C: 52.57 (OCH_3), 116.49 (=CH); 120.90, 127.85, 129.30,

and 129.34 (8 CH, ortho and meta, arom.); 125.25 and 129.18 (2 CH, para, arom.); 133.98 and 147.32 (2 C, ipso, arom.); 141.42 (=CS); 151.57 (C=N); 164.56 and 166.36 (2 C=O).

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

Light yellow crystals, m. p. 87.5–88.5, yield 64%. IR (KBr) (υ_{max}, cm^{-1}): 3060, 2923, 1723, 1646, 1377, 1315, 1200, 769, 700, and 585. ^{1}H NMR ($CDCl_3$)δ_H: 1.34 (3 H, t, $^3J_{HH}$ = 7.1 Hz, CH_3); 4.28 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2); 6.96 (2 H, d, $^3J_{HH}$ = 7.5 Hz, arom.); 6.99 (1 H, s, =CH); 7.1–7.6 (8 H, m, arom.). ^{13}C NMR ($CDCl_3$) δ_C: 14.14 (CH_3); 61.78 (OCH_2); 116.95 (=CH); 120.90, 127.85, 129.28, and 129.35 (8 CH, ortho and meta, arom.); 125.21 and 129.17 (2 CH, para, arom.); 133.97 and 147.34 (2 C, ipso, arom.); 141.13 (=CS); 151.77 (C=N); 164.63 and 165.98 (2 C=O).

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