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Microwave Assisted, One Pot Synthesis of Alkyl-3-amino-2-arylimino-1,3-thiazolan-4-ones-5-ylidene Acetate

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Reaction of 4-phenylthiosemicarbazide and thiosemicarbazide with dialkyl acetylene dicarboxylate in CH_2Cl_2 at microwave irradiation lead to alkyl-3-amino-2-phenyliminothiazolidine-4-one-5-ylidene acetate and alkyl-3-amino 2-iminothiazolidine-4-one-5-ylidene acetate in moderate yields and short times. Di-*t*-butylacetylenedicarboxylate have a different treatment and the cyclization products is not observed. The structures of the synthesized compounds were elucidated by elemental analysis and spectral data.

Key Words: Microwave irradiation, Thiazolidine-4-one, 4-Phenylthiosemicarbazide, Thiosemicarbazide.

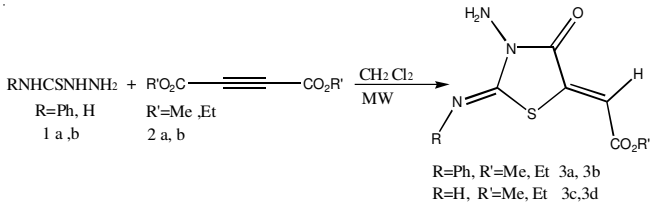
INTRODUCTION

The synthesis of the thiazolidin-4-one scafold is gaining considrable attention due to the fact that its derivatives have shown a wide spectrum of activities. Thiazolidine-4-ones are important building blocks in pharmaceutical agent and biologically active products[1-5]. Several substituted thiazolidinones have been found to possess hypnotic, anaesthetic, sedative, anticonvulsant and microbiological activities[6-9]. Some thiazoline-4-ones derivatives are reported as human immunodeficiency virus-1 (HIV-1) non-nucleoside reverse transcriptase inhibitors (NNRTIs) or anticancer activities and can inhibit cell division[10-30]. In view of the various physiological activities of thiazolidinones, many thiazolidinone derivatives have been prepared and several new methods for the preparation of substituted thiazolidine-4-one have been recently reported[31-34]. However,these methods have several drawbacks, namely, the need for a high reaction temperature and long reaction time. The development of mild and efficient methods is still desired. We present here a mild and efficient method to give 2-iminothiazolidine-4-ones-5-ylidene acetate in good yields and short times.

EXPERIMENTAL

Compounds were obtained from merck and used without further purification. The melting points were taken on an electrothermal 9100 capillary melting point apparatus and are uncorrected. Thin-layer chromatographies were performed using HF_{254} fluorescent silica gel plates (Merck), which were examined under UV 254 and 365 nm light. Infrared spectra (ν/cm^{-1}) were recorded on Shimadzu IR-470, using KBr disks. ^1H and ^{13}C NMR spectra were recorded on DRX-500 MHz NMR Spectrometer at 293 K in $CDCl_3$. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus,operating at a frequency of 2.45 GHz with continuous irradiation of 300 W maximum power.

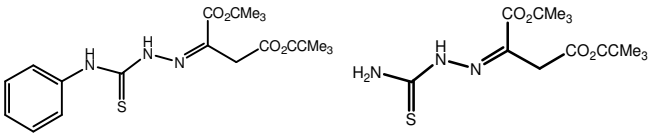
Synthesis of (3a-d): 4-Phenylthiosemicarbazide (2 mmol) (**1a**) was mixed with dialkyl acetylenedicarboxylate (2 mmol) in dry CH_2Cl_2 (5 mL) and irradiated in a microwave oven at 300 W for 10 min. Then the reaction mixture was cooled and recrystallaized with ethanol. The pure products identified as alkyl-3-amino-2 phenyliminothiazolidine-4-one-5-ylidene-acetate (**3a**) in reasonable yields (**Scheme-I**).



Scheme-I: Synthesis of alkyl-3-amino-2-phenyliminothiazolidine-4-one-5-ylidene acetate

In the same method thiosemicarbazide reacted with dialkyl acetylenic esters and produce the same derivatives of thiazolidin-4-ones (**3c-3d**) in excellent yields (**Scheme-I**).

Surprisingly di-*tert*-butyl acetylene dicarboxylate have different treatment and instead of cyclization product, we isolated condensation product and thiosemicarbazon derivatives are chief products (**Scheme-II**).



Scheme-II: Product of 4-Phenylthiosemicarbazide and thiosemicarbazide with di-*tert*-butyl acetylene dicarboxylate

RESULTS AND DISCUSSION

In our continuous approach toward developing biologically active heterocyclic synthesis *via* acetylenic esters-based reactions involving CH-, NH- or OH-acid compounds[30-34], herein we wish to explain an expedient method for construction of some novel 2-imino-thiazolidine-4-one-5-ylidene acetate derivatives (**3**) from one-pot reaction between 4-phenylthiosemicarbazide (**1a**) and thiosemicarbazide (**1b**) with appropriate acetylenic esters (**2**) in good yields (**Scheme-I**).

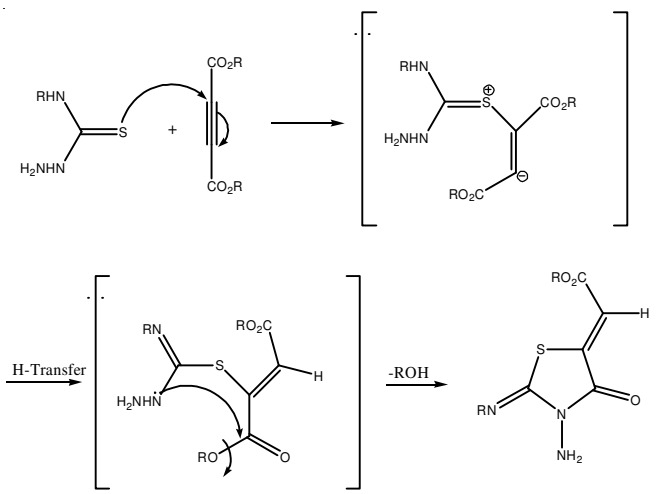
Methyl-3-amino-2-Phenylimino-4-oxo-1,3-thiazolan-5-ylidene acetate (3a): Pale yellow crystals; yield: 72 %, m.p. 162-163 ºC. IR (KBr, ν_{max}, cm^{-1}): 3316, 3125 (NH_2), 1728, 1635 (2C=O), 1684 (C=C), 1610 (C=N). ^{1}H NMR: δ = 3.80 (s, MeO), 4.79 (s, NH_2), 7.08 (s, CH), 7.13-7.66 (5H, Ph) ppm. ^{13}C NMR: δ = 168.1, 160.1 (2C=O), 152.6 (C=N), 143.1 (C), 136.2 (C), 128.1 (2CH), 126.8 (CH), 123.7 (2CH), 114.3 (CH), 51.0 (MeO) ppm. MS:m/z (%) = 277 (28, M^+), 160 (8), 142 (1), 117 (23), 85 (86), 77 (100), 58 (63), 44 (24). Anal calcd. for $C_{12}H_{11}N_3O_3S$ (277.24): C, 51.19; H, 3.96; N, 15.14 %. Found: C, 51.71; H, 3.77; N, 15.43 %.

Ethyl-3-amino-2-phenylimino-4-oxo-1,3-thiazolan-5-ylidene acetate (3b): Pale yellow powder; yield: 72 %, m.p.: 162-164 ºC. IR (KBr, ν_{max}, cm^{-1}): 3309, 3146 (NH_2), 1719, 1642 (2C=O), 1688 (C=C), 1593 (C=N). ^{1}H NMR: δ = 1.38 (t, $^3J_{HH}$ = 7.3, Me), 4.18 (q, $^3J_{HH}$ = 7.2, CH_2O), 4.55 (brs, NH_2), 6.78 (s, CH), 7.03-7.49 (5H, Ph) ppm. ^{13}C NMR: δ = 162.2, 160.9 (2C=O), 146.7 (C=N), 146.0 (C), 138.5 (C), 127.9 (2CH), 124.0 (CH), 120.5 (2CH), 115.8 (CH), 62.9 (CH_2O), 14.7 (CH_3) ppm. MS: m/z (%) 291 (24, M^+), 264 (4), 142 (23), 135 (26), 107 (40), 5 (66), 77 (100), 57 (20), 44 (54). Anal. calcd. for $C_{13}H_{13}N_3O_3S$ (291.28): C, 53.55; H, 4.46; N, 14.01 %. Found: C, 51.38; H, 4.73; N, 16.01 %.

Methyl-3-amino-2-imino-4-oxo-1,3-thiazolan-5-ylidene acetate (3c): Yellow crystals; yield: 89 %, m.p. 180-181 ºC. IR (KBr, ν_{max}, cm^{-1}): 3300, 3167 (NH_2), 1742, 1649 (2C=O), 1654 (C=C), 1606 (C=N). ^{1}H NMR: δ = 3.80 (s, MeO), 4.81 (s, NH_2), 5.20 (s, NH), 7.11 (s, CH), ppm. ^{13}C NMR: δ = 164.2, 160.8 (2C=O), 145.6 (C=N), 141.1 (C), 133.8 (C), 122.3 (CH), 51.3 (MeO) ppm. MS: m/z (%) 201 (38, M^+), 170 (8), 142 (5), 126 (25), 85 (86), 56 (100), 44 (24). Anal. calcd. for $C_6H_7N_3O_3S$ (201.3): C, 35.82; H, 3.48; N, 20.89 %. Found: C, 35.74; H, 3.17; N, 21.74 %.

Ethyl-3-amino-2-imino-4-oxo-1,3-thiazolan-5-ylidene acetate (3d): Green yellow powder; yield: 96 %, m.p. 170-171 ºC. IR (KBr, ν_{max}, cm^{-1}): 3294, 3153 (NH_2), 1727, 1648 (2C=O), 1680 (C=C), 1596 (C=N). ^{1}H NMR: δ = 1.33 (t, $^3J_{HH}$ = 7.1, Me), 4.36 (q, $^3J_{HH}$ = 7.1, CH_2O), 4.80 (brs, NH_2), 5.21 (s, NH), 6.94 (s, CH) ppm. ^{13}C NMR: δ = 166.2, 163.9 (2C=O), 146.7 (C=N), 142.9 (C), 137.5 (C), 121.0 (CH), 60.5 (CH_2O), 16.4 (CH_3) ppm. MS: m/z (%) 215 (28, M^+), 170 (14), 142 (36), 135 (26), 107 (40), 85 (100), 57 (20), 44 (54). Anal. calcd. for $C_7H_9N_3O_3S$ (215.21): C, 39.01; H, 4.18; N, 19.53 %. Found: C, 38.48; H, 4.13; N, 21.41 %.

The structures of compounds were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z- values. The ^{1}H NMR spectrum, of **3a** in $CDCl_3$ showed three singlets for methoxy δ = 3.80, amino δ = 4.79 and olefinic δ = 7.08 protons δ, along with multiplets δ = 7.13 - δ = 7.66 for the aromatic protons. The ^{13}C NMR spectra of **3a** showed ten signals in agreement whit the proposed structure. Partial assignments of these resonance are given in the experimental section. The ^{1}H and ^{13}C NMR spectra of **3b-3d** are similar to those for **3a**, except for the ester and aryl moieties, which exhibit characteristic signals at appropriate chemical shift. On the basis of well established chemistry of electrophilic acetylenes it is reasonable to assume that compounds **3** results from the initial conjugate addition of the sulfur atom of **1** to the acetylenic ester and the subsequent conversion of the 1:1 adduct to **3**. Then the ester group of intermediate **3** is attacked by the amino moiety to yield **3** by elimination of ROH (**Scheme-III**). When the bulky di-*t*-butylacetylenedicarboxylate is used, the steric hindrance prevent the usual mechanism and the adduct product is not reasonable. In conclusion, we have prepared novel thiazolidine-4-one derivatives *via* one-pot reaction between 4-phenylthiosemicarbazide and thiosemicarbazide with dialkyl acetylene dicarboxylate. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification.



Scheme-III: Mechanism of reaction

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