A Simple and Efficient Synthesis of Some Novel Thiazolidine-4-one Derivatives

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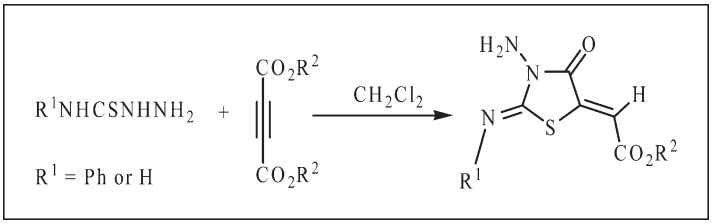

Reaction of 4-phenylthiosemicarbazide with dialkyl acetylenedicarboxylate in CH_2Cl_2 at 0°C lead to construction of alkyl 3-amino-2-phenyliminothiazolidine-4-one-5-ylidene acetate in a few minutes and good yields. Alternatively, the use of thiosemicarbazide has given the corresponding 3-amino-2-imino-thiazolidine-4-one-5-ylidene acetate, while application of di-*t*-butylacetylenedicarboxylate in these reactions has not entailed with cyclization.

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INTRODUCTION

Thiazolidine-4-ones are important building blocks in variety of pharmaceutical agents and biologically active products [1]. Several substituted thiazolidinones have been found to possess hypnotic, anesthetic, sedative, anticonvulsant, and microbiological activities [2–4]. Some thiazoline derivatives show interesting anti-HIV or anticancer activities and can inhibit cell division [5–10]. Because 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 [11,12]. Despite the synthetic importance of these methods, they commonly suffer from the need to elevated temperatures and also from long reaction times. Therefore, it is reasonable that development of mild and efficient methods for their synthesis still is more desired. In this context, we present here a mild and expedient method for synthesis of 2-iminothiazolidine-4-one-5-ylidene acetate derivatives in fairly good yields.

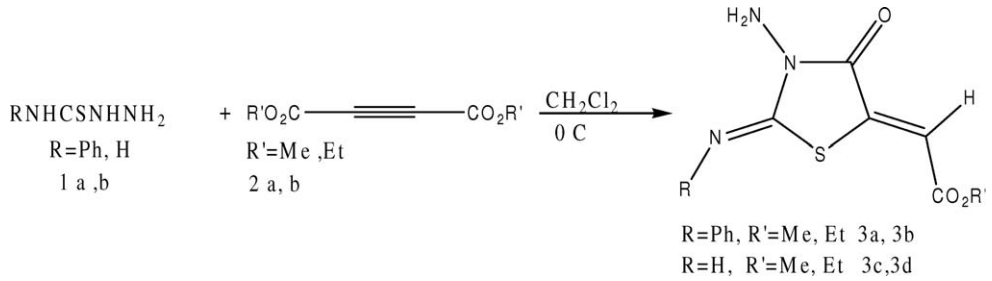
RESULTS AND DISCUSSION

As is shown in Scheme 1, the synthesis of 2-imino-thiazolidine-4-one-5-ylidene acetate was simply effected by a two component reaction between thiosemicarbazide and an acetylenic ester. The reaction proceeds smoothly without using any catalyst by mixing the two reactants in dry CH_2Cl_2 media at room temperature and needs no more care on controlling the temperature or using special techniques of activation. Only the thiazolidine products were formed and separated from the reaction mixture. An attracting feature of this reaction is the synthesis of a multifunctionalized complex heterocycle from simple starting materials.

Thus, 4-Phenylthiosemicarbazide **(1a)** and dimethyl acetylenedicarboxylate undergo a smooth reaction in dry CH_2Cl_2 at 0°C to produce methyl 3-amino-2 phenylimino-thiazolidine-4-one-5-ylidene acetate **(3a)** in 94% yield (Scheme 1). In a similar manner, thiazolidine-4-ones **(3c,d)** were formed on reaction between thiosemicarbazide and the corresponding acetylenic ester in excellent yields (Scheme 1). Surprisingly, di-*tert*-butyl acetylenedicarboxylate showed up a different behavior as instead of cyclocondensation with thiosemicarbazide their reaction lead to addition of the two components and solely formation of thiosemicarbazone derivatives (Scheme 2).

Structures of all the compounds were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data as well as elemental analyses. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^{1}H NMR spectrum of **3a**, for example, in $CDCl_3$ showed three singlet peaks arising from resonances of methoxy δ 3.48, amino δ 4.89, and olefinic protons δ 7.00, along with multiplets at δ 7.03–7.42 ppm for the aromatic protons. The ^{13}C NMR

Scheme 1



spectrum of **3a** showed 10 signals in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section. The ^{1}H- and ^{13}C NMR spectra of **3b–3d** are very similar to those of **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 [10], it is reasonable to assume that the synthesis proceeds through initial conjugate addition of the sulfur atom of **1** onto the acetylenic ester following cyclocondensation of the thus formed 1:1 adduct [13,14] to yield the products **3** (Scheme 3).

In the cases of using di-*t*-butyl acetylenedicarboxylate, the reactions are prevented from proceeding through above mechanism due to steric hindrance of bulky alkyl groups, so are unable to give the desired thiazolidine products.

In conclusion, we have made a contribution to the synthesis of thiazolidine-4-one compounds [13,14] by using the reaction between 4-phenylthiosemicarbazide or thiosemicarbazide with a dialkyl acetylenedicarboxylate to produce some novel thiazolidine-4-one derivatives. The method carries the advantage that is not only the reaction performed under neutral conditions but also the substrates can react by mixing without any activation or modification.

EXPERIMENTAL

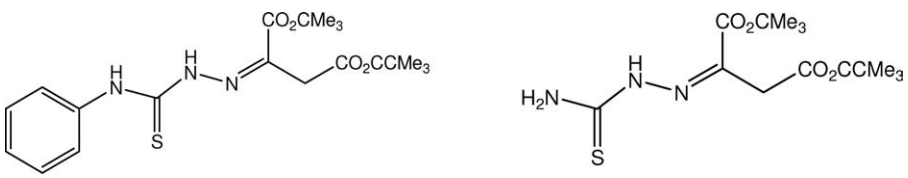
Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded by a Bruker DRX-300 AVANCE instrument with deuteriochloroform as solvent at 300 and 75 MHz, respectively. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. 4-Phenylthiosemicarbazide, thiosemicarbazide, dimethyl acetylenedicarboxylate, and diethyl acetylenedicarboxylate were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

Typical procedure for the preparation of compounds 3. To a stirred solution of **1** (2 mmol) in 10 mL of dichloromethane was added dropwise a mixture of **2** (2 mmol) in 2 mL dichloromethane at 0°C over 1 min. The reaction quickly went to complete, as monitored by tlc on silica-gel 60 using 1:1 solution of ethyl acetate:petroleum ether, and the solid product precipitate. After 5 min, the solid was filtered and recrystallized from diethyl ether to afford the pure products.

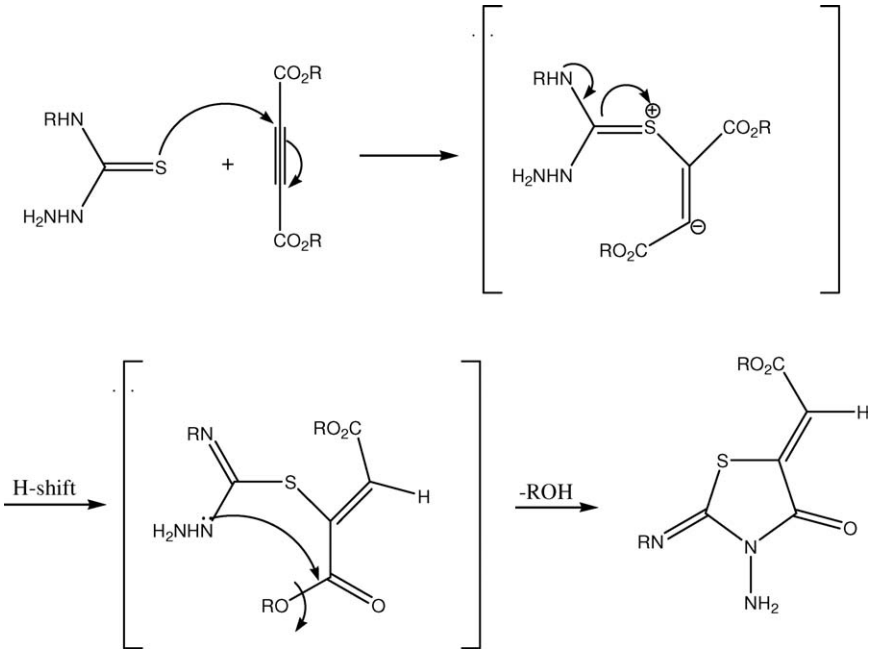
Methyl 3-amino-2-phenylimino-4-oxo-1,3-thiazolan-5-ylideneacetate (3a). Pale yellow crystals; yield: 0.55g (99%), mp 161–162°C; IR (KBr): $\bar{\nu}$ = 3306, 3145 (NH_2), 1731, 1645 (C=O), 1694 (C=C), 1608 (C=N) cm^{-1}; ^{1}H NMR: δ = 3.84 (3H, s, MeO), 4.89 (2H, s, NH_2), 7.0 (1H, s, CH), 7.03–7.42 (5H, m, Ph) ppm; ^{13}C NMR: δ = 166.6, 161.8 (C=O), 149.6 (C=N), 146.8 (C), 139.8 (C), 129.9 (2CH), 126.0 (CH), 121.5 (2CH), 117.3 (CH), 53.0 (CH_3—O) 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, 51.33; H, 3.87; N, 15.05%.

Ethyl 3-amino-2-phenylimino-4-oxo-1,3-thiazolan-5-ylideneacetate (3b). Pale yellow powder; yield: 0.57 g (98%), mp 160–163°C; IR (KBr): $\bar{\nu}$ = 3299, 3146 (NH_2), 1729, 1642 (C=O), 1688 (C=C), 1593 (C=N) cm^{-1}; ^{1}H NMR: δ = 1.33 (3H, t, $^{3}J_{HH}$ = 7.1, Me), 4.28 (2H, q, $^{3}J_{HH}$ = 7.1, CH_2O), 4.88 (2H, br s, NH_2), 6.99 (1H, s, CH), 7.03–7.39 (5H, m, Ph) ppm; ^{13}C NMR: δ = 166.2, 161.9 (2C=O), 149.7 (C=N), 146.9 (C), 139.5 (C), 129.9 (2CH), 126.0 (CH), 121.5 (2CH), 117.8 (CH), 62.3 (CH_2O), 14.5 (CH_3) ppm; ms: m/z (%) 291 (24,

Scheme 2



Scheme 3



M^+), 264 (4), 142 (23), 135 (26), 107 (40), 85 (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, 51.78; H, 4.83; N, 14.39%.

Di-t-butyl succinal-2-ylidene-4-phenylthiosemicarbazone (4a). Greenish white powder; yield: 0.74 g (95%), mp 152–153°C; IR (KBr): $\bar{\nu}$ = 3286, 3271 (NH), 1721, 1685 (2 C=O), 1598 (C=N), 1584 (C=S) cm^{-1}; ^1H NMR: δ = 1.50 (9H, s, $3CH_3$), 1.57 (9H, s, $3CH_3$), 3.44 (2H, s, CH_2), 7.25–7.70 (5H, m, Ph), 9.31 (1H, s, NH), 12.55 (1H, s, NH) ppm;^{13}C NMR: δ = 176.7 (C=S), 169.2, 161.2 (2C=O), 138.0 (C=N), 131.0 (C), 129.1 (2CH), 126.6 (C), 124.4 (2CH), 85.1 (C) 82.2 (C), 41.4 (CH_2), 28.5 ($3CH_3$), 28.30 ($3CH_3$) ppm; ms: m/z (%) 393 (8, M^+), 292 (70), 264 (28), 236 (100), 190 (18), 151 (18), 136 (44), 57 (88). *Anal*. Calcd. for $C_{19}H_{27}N_3O_4S$ (393.12): C, 58.01; H, 6.87; N, 10.68%. Found: C, 58.37; H, 6.89; N, 11.01%.

Methyl3-amino-2-imino-4-oxo-1,3-thiazolan-5-ylideneacetate (3c). Yellow crystals; yield: 0.36 g (89%), mp 181–182°C; IR (KBr): $\bar{\nu}$ = 3302, 3147 (NH_2), 1732, 1646 (2 C=O), 1694 (C=C), 1608 (C=N) cm^{-1}; ^1H NMR: δ = 3.86 (s, MeO), 4.85 (s, NH_2), 5.2(s, NH), 7.01 (s, CH), ppm; ^{13}C NMR: δ = 166.2, 162.8 (2 C=O), 148.6 (C=N), 146.1 (C), 139.8 (C), 126.3 (CH), 52.3 (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, 35.34; H, 3.27; N, 21.44%.

Ethyl3-amino-2-imino-4-oxo-1,3-thiazolan-5-ylideneacetate (3d). Greenish yellow powder; yield: 0.39 g (91%), mp 170–173 °C; IR (KBr): $\bar{\nu}$ = 3291, 3143 (NH_2), 1727, 1643 (2 C=O), 1685 (C=C), 1591 (C=N) cm^{-1}; ^1H NMR: δ = 1.32 (t, $^3J_{HH}$ = 7.1, Me), 4.26 (q, $^3J_{HH}$ = 7.1, CH_2O), 4.88 (br s, NH_2),5.11(s, NH), 6.90 (s, CH) ppm;^{13}C NMR: δ = 166.2, 161.9 (2 C=O), 149.7 (C=N), 146.9 (C), 139.5 (C), 126.0 (CH), 62.5 (CH_2O), 14.4 (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, 38.88; H, 4.13; N, 20.11%.

Di-t-butyl succinal-2-ylidenethiosemicarbazone (4b). White powder; yield: 0.54g (85%), mp 162–163°C; IR (KBr): $\bar{\nu}$ = 3286, 3273 (NH), 1724, 1685 (2 C=O), 1595 (C=N), 1584 (C=S) cm^{-1}; ^1H NMR: δ = 1.52 (9H, s, $3CH_3$), 1.55 (9H, s, $3CH_3$), 3.48 (2H, s, CH_2), 9.35 (2H, s, NH_2), 12.50 (1H, s, NH) ppm;^{13}C NMR: δ = 176.7 (C=S), 169.2, 161.2 (2 C=O), 138.0 (C=N), 85.8 (C) 82.1 (C), 41.6 (CH_2), 28.9 (3 CH_3), 28.38 (3 CH_3) ppm; ms: m/z (%) 317 (18, M^+), 216 (77), 200 (22), 156 (100), 99 (18). *Anal*. Calcd. for $C_{13}H_{23}N_3O_4S$ (317.12): C, 49.21; H, 7.25; N, 13.24%. Found: C, 49.37; H, 7.89; N, 14.01%.

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