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RESEARCH ARTICLE

Efficient synthesis of functionalized bis-(4-oxo-1,3-thiazolan-5-ylidene)acetates

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Reaction of 1-(2,2-dimethyl-propionyl)-3-{4-[3-(2,2-dimethyl-propionyl)thioureido]phenyl}thiourea or 1-(2,2-dimethyl-propionyl)-3-{5-[3-(2,2-dimethyl-propionyl)thioureido]naphthalen-1-yl}thiourea with dialkyl acetylenedicarboxylates in CH_2Cl_2 leads to alkyl (2-(2,2-dimethyl-propionylimino)-3-{4-[2-(2,2-dimethyl-propionylimino)-5-alkoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]-phenyl}-4-oxo-thiazolidin-5-ylidene)acetates or alkyl (2-(2,2-dimethyl-propionylimino)-3-{5-[2-(2,2-dimethyl-propionylimino)-5-alkoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]naphthalen-1-yl}-4-oxo-thiazolidin-5-ylidene)acetates in good yields.

Keywords: Thiazolidin-4-one; Pivaloylisothiocyanate; 1-Aryl-3-alkylcarbonylthioureas; 1,4-Phenylenediamine; 1,5-Naphthalenediamine; Acetylenic ester; Heterocyclic synthesis

1. Introduction

Thiazolidine-4-ones are well known for their pharmacological activities [1]. Several substituted thiazolidinones have been found to possess hypnotic, anaesthetic, sedative, anticonvulsant and microbiological activities [2–4]. Some thiazoline derivatives show interesting anti-HIV or anticancer activities and can inhibit cell division [5–9]. In view of the various physiological activities of thiazolidinones, many thiazolidinone derivatives have been prepared [1, 10, 11]. The reaction of thiourea with acetylenic esters has been variously reported to give a thiazolin-4-one (**1**), an imidazolinthion (**2**), or a 1,3-thiazin-4-one (**3**) (scheme 1) [10]. However, latter studies have shown that in fact it is the thiazolin-4-one (**1**) that is formed in this reaction [10].

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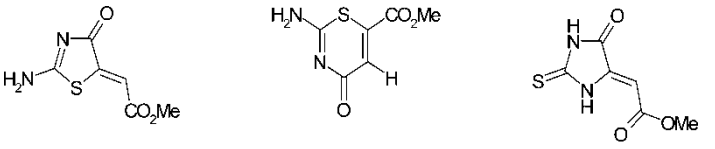

SCHEME 1

As part of our current studies on the development of new routes in heterocyclic synthesis [12–19], we wish to report a simple synthesis of bis-(4-oxo-1,3-thiazolan-5-ylidene)-acetates. Thus, 1,4-phenylenediamine (**4**) or 1,5-naphthalenediamine (**5**) was allowed to react with pivaloylisothiocyanate (**6**) in CH_2Cl_2 at room temperature, to produce 1-(2,2-dimethyl-propionyl)-3-{4-[3-(2,2-dimethyl-propionyl)thioureido]phenyl}thiourea (**7**) or 1-(2,2-dimethyl-propionyl)-3-{5-[3-(2,2-dimethyl-propionyl)thioureido]naphthalen-1-yl} thiourea (**8**) (scheme 2).

Reaction of **7** or **8** with dialkyl acetylenedicarboxylates (**9**) in CH_2Cl_2 leads to alkyl 2-(2,2-dimethyl-propionylimino)-3-{4-[2-(2,2-dimethyl-propionylimino)-5-alkoxycarbonyl methylene-4-oxo-thiazolidin-3-yl]phenyl-4-oxo-thiazolidin-5-ylidene}acetates **10a–10b** or alkyl 2-(2,2-dimethyl-propionylimino)-3-{5-[2-(2,2-dimethyl-propionylimino)-5-alkoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]naphthalen-1-yl-4-oxo-thiazolidin-5-ylidene}acetates **10c–10d** in good yields (scheme 3).

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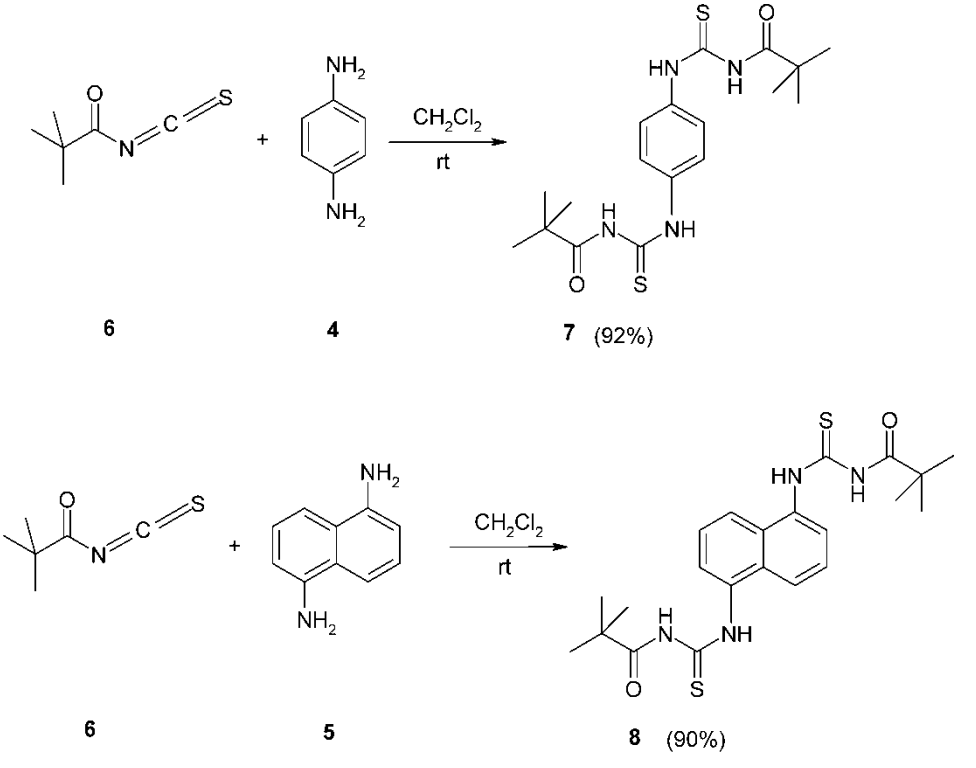
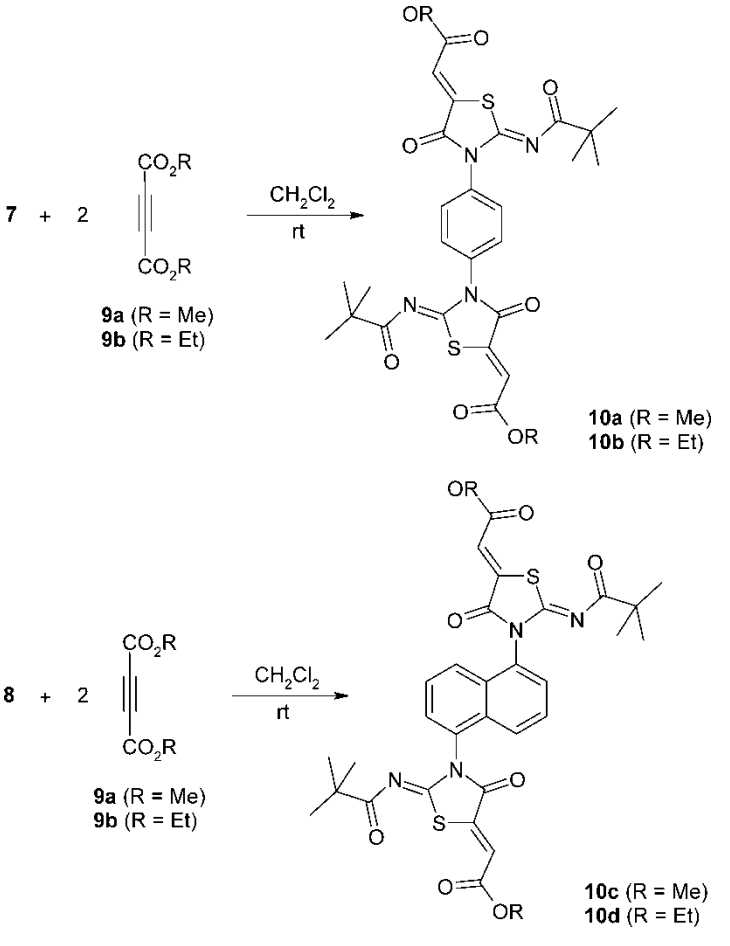


SCHEME 2



SCHEME 3

2. Results and discussion

Dimethyl acetylenedicarboxylate (**9a**) undergoes a smooth reaction with **8** in CH_2Cl_2 at room temperature to produce methyl 2-(2,2-dimethyl-propionylimino)-3-{4-[2-(2,2-dimethyl-propionylimino)-5-methoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]phenyl-4-oxo-thiazolidin-5-ylidene}acetate (**10a**) in 88% yield.

The structure of **10a** was deduced from its elemental analyses and its IR, ^{1}H- and ^{13}C NMR spectra. The mass spectrum of this compound displayed molecular ion peak at $m/z = 614$. The ^{1}H NMR spectrum of **10a** in $CDCl_3$ showed four singlets for *tert*-butyl ($\delta = 1.13$), methoxy ($\delta = 3.92$), olefinic ($\delta = 7.09$), and aromatic ($\delta = 7.52$) protons. The ^{13}C NMR spectrum of **10a** showed eleven signals in agreement with the proposed structure. Partial assignments of these resonances are given in the Experiment section. The ^{1}H- and ^{13}C NMR spectra of **10b**–**10d** are similar to those for **10a**, except for the alkoxy and aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

The methylcarboxymethylidene moiety for the derivatives **1** and **3** (scheme 1) has to be in *Z*-configuration. Such *Z*-configuration is widely discussed in literature.[1] The ^{1}H NMR spectra for compounds **10a**–**10d** exhibited the methylidene proton signals near 7.0 ppm, which is also consistent with *Z*-configuration.

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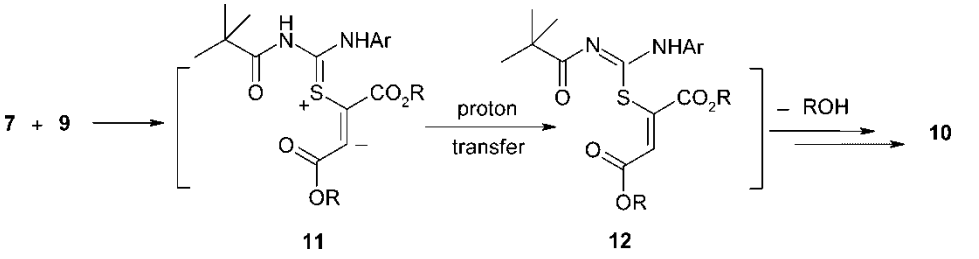

SCHEME 4

On the basis of well-established chemistry of electrophilic acetylenes [1, 10], it is reasonable to assume that compounds **10** result from the initial conjugate addition of the sulfur atom of **7** (or **8**) to the acetylenic ester and the subsequent conversion of the 1 : 1 adduct to **12**. Then, the ester group of intermediate **12** is attacked by the amino moiety to yield the 4-oxo-1,3-thiazolan-5-ylidene ring system by elimination of ROH. This sequence is repeated for construction of the second five-membered ring in **10** (see scheme 4).

In summary, we have prepared novel bis-(4-oxo-1,3-thiazolan-5-ylidene)acetates via reaction between 1-(2,2-dimethyl-propionyl)-3-{4-[3-(2,2-dimethyl-propionyl)thioureido] phenyl}thiourea or 1-(2,2-dimethyl-propionyl)-3-{5-[3-(2,2-dimethyl-propionyl)thioureido] naphthalen-1-yl}thiourea with dialkyl acetylenedicarboxylates. 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. The bis-thiazolidine-4-ones **10** may be considered as potentially useful synthetic intermediates.

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3. Experiment

3.1 *General*

1-Aryl-3-alkylcarbonylthioureas were prepared by a known procedure [20]. Compounds **4**, **5**, **6** and **9** were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; δ in ppm, J in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in m/z. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

3.2 *General procedure for the preparation of compounds 7 and 8*

To a stirred solution of **7** (2 mmol) in 10 mL of CH_2Cl_2 was added drop wise a mixture of **4** (or **5**) (2 mmol) in 5 mL of CH_2Cl_2 at 0 °C over 5 min. The reaction was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under reduced pressure, and the residue was recrystallized from Et_2O to afford the pure adducts.

3.3 *1-(2,2-dimethyl-propionyl)-3-{4-[3-(2,2-dimethyl-propionyl)thioureido]phenyl}thiourea (7)*

White powder; yield: 0.72 g (92%), mp 224–226 °C. IR (KBr): 3251, 3155 (2 NH), 1698 (C=O), 1520, 1156, 1131. ^{1}H NMR: 1.34 (s, 2 CMe_3), 7.76 (s, C_6H_4), 8.55 (s, 2 NH), 12.60

(s, 2 NH). ^{13}C NMR: 27.4 (2 C*Me*$_3$), 40.4 (2 *C*Me$_3$), 124.5 (4 CH of C_6H_4), 136.2 (2 C of C_6H_4), 178.7, 179.8 (C=O, C=S). EI-MS: 394 (2, M^+), 350 (13), 337 (25), 309 (9), 250 (17), 144 (25), 85 (43), 57 (100), 41 (35). Anal. calc. for $C_{18}H_{26}N_4O_2S_2$ (394.55): C 54.79, H 6.64, N 14.20%; found: C 54.46, H 6.72, N 14.44%.

3.4 *1-(2,2-dimethyl-propionyl)-3-{5-[3-(2,2-dimethyl-propionyl)thioureido]naphthalen-1-yl}thiourea (8)*

White powder; yield: 0.80 g (90%), mp 223–225 °C. IR (KBr): 3432, 3121 (2 NH), 1678 (C=O), 1524, 1319, 1154, 1133. ^{1}H NMR: 1.40 (s, 2 CMe$_3$), 7.63 (dd, ^3J = 8.1 and 7.5, 2 CH), 7.98 (d, ^3J = 8.1, 2 CH), 8.06 (d, ^3J = 7.5, 2 CH), 8.74 (s, 2 NH), 12.69 (s, 2 NH). ^{13}C NMR: 27.5 (2 C*Me*$_3$), 40.5 (2 *C*Me$_3$), 122.0 (2 CH), 124.9 (2 CH), 126.7 (2 CH), 129.7 (2 C), 134.6 (2 C), 180.1, 180.7 (C=O, C=S). EI-MS: 444 (3, M^+), 400 (18), 387 (23), 359 (16), 300 (13), 144 (30), 85 (27), 57 (100), 41 (23). Anal. calc. for $C_{22}H_{28}N_4O_2S_2$ (444.62): C 59.43, H 6.35, N 12.60%; found: C 59.76, H 6.62, N 12.74%.

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3.5 *General procedure for the preparation of compounds 10*

To a stirred solution of **7** (or **8**) (2 mmol) in 10 mL of CH_2Cl_2 was added drop wise a mixture of **9** (2 mmol) in 5 mL of CH_2Cl_2 at 0 °C over 5 min. The reaction was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under reduced pressure, and the residue was recrystallized from Et_2O to afford the pure adducts.

3.6 *Methyl 2-(2,2-Dimethyl-propionylimino)-3-{4-[2-(2,2-dimethyl-propionylimino)-5-methoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]phenyl-4-oxo-thiazolidin-5-ylidene}acetate (10a)*

Pale yellow powder; yield: 1.08 g (88%), mp 280–282 °C. IR (KBr): 1721, 1675, 1607 (3 C=O), 1151 (C=C), 1101 (C−S). ^{1}H NMR: 1.13 (s, 2 CMe$_3$), 3.92 (s, 2 MeO), 7.09 (2 H, s, 2 CH=C), 7.52 (s, C_6H_4). ^{13}C NMR: 27.0 (2 C*Me*$_3$), 42.6 (2 *C*Me$_3$), 53.2 (2 MeO), 120.8 (2 CH), 128.8 (4 CH of C_6H_4), 134.7 (2 C), 141.0 (2 C), 164.2, 165.0, 165.8 (2 C=O, C=N), 192.1 (C=O). EI-MS: 614 (2, M^+), 584 (26), 500 (7), 316 (6); 172 (30); 85 (31), 57 (100), 41 (39). Anal. calc. for $C_{28}H_{30}N_4O_8S_2$ (614.68): C 54.71, H 4.92, N 9.12%; found: C 54.44, H 4.77, N 9.34%.

3.7 *Ethyl (2-(2,2-Dimethyl-propionylimino)-3-{4-[2-(2,2-dimethyl-propionylimino)-5-ethoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]phenyl-4-oxo-thiazolidin-5-ylidene}acetate (10b)*

Pale yellow powder; yield: 1.09 g (85%), mp 262.5–264 °C. IR (KBr): 1731, 1695, 1611 (3 C=O), 1555 (C=C), 1099 (C−S). ^{1}H NMR: 1.13 (s, 2 CMe$_3$), 1.39 (t, ^3J = 7.2, 2 Me), 4.37 (q, ^3J = 7.2, 2 CH_2O), 7.08 (s, 2 CH=C), 7.52 (s, C_6H_4). ^{13}C NMR: 14.6 (2 Me), 27.0 (2 C*Me*$_3$), 42.6 (2 *C*Me$_3$), 62.4 (2 CH_2O), 121.3 (2 CH), 128.9 (4 CH of C_6H_4), 134.7 (2 C), 140.7 (2 C), 164.2, 165.0, 165.4 (2 C=O, C=N), 192.1 (C=O). EI-MS: 642 (1, M^+), 612 (13), 528 (16), 344 (27), 172 (18), 85 (43), 57 (100), 41 (47). Anal. calc. for $C_{30}H_{34}N_4O_8S_2$ (642.73): C 56.06, H 5.33, N 8.72%; found: C 56.43, H 5.42, N 8.94%.

3.8 *Methyl (2-(2,2-Dimethyl-propionylimino)-3-{5-[2-(2,2-dimethyl-propionylimino)-5-methoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]naphthalen-1-yl-4-oxo-thiazolidin-5-ylidene}acetate (10c)*

Pale yellow powder; yield: 1.25 g (94%), mp 299–301 °C. IR (KBr): 1742, 1699, 1675 (3 C=O), 1098 (C-S). ^{1}H NMR: 0.90 (s, 2 CMe_3), 3.94 (s, 2 MeO), 7.14 (s, 2 CH), 7.50 (dd, $^3J = 6.3, ^4J = 2.0$, $H_{2,6}$ of $C_{10}H_6$), 7.60–7.69 (m, 4 CH of $C_{10}H_6$). ^{13}C NMR: 26.8 (2 CMe_3), 42.5 (2 CMe$_3$), 53.2 (2 MeO), 121.1 (2 CH), 124.8 (2 CH), 127.2 (2 CH), 127.7 (2 CH), 130.8 (2 C), 132.1 (2 C), 141.2 (2 C−N), 164.3, 165.3, 165.9 (2 C=O, C=N), 192.2 (C=O). EI-MS: 664 (2, M^+), 620 (8), 607 (11), 522 (12), 336 (35), 311 (17), 186 (21), 57 (100), 41 (43). Anal. calc. for $C_{32}H_{32}N_4O_8S_2$ (664.74): C 57.82, H 4.85, N 8.43%; found: C 57.53, H 4.74, N 8.64%.

3.9 *Ethyl (2-(2,2-Dimethyl-propionylimino)-3-{5-[2-(2,2-dimethyl-propionylimino)-5-ethoxycarbonylmethylene-4-oxo-thiazolidin-3-yl]naphthalen-1-yl-4-oxo-thiazolidin-5-ylidene}acetate (10d)*

Pale yellow powder; yield: 1.19 g (86%), mp 214–216 °C. IR (KBr): 1728, 1702, 1670 (3 C=O), 1195 (C=N), 1159. ^{1}H NMR: 0.90 (s, 2 CMe_3), 1.41 (t, $^3J = 7.1$, 2 Me), 4.40 (q, $^3J = 7.1$, 2 CH_2O), 7.14 (s, 2 CH), 7.51 (dd, $^3J = 6.2$, $^4J = 2.0$, $H_{2,6}$ of $C_{10}H_6$), 7.61–7.68 (m, 4 CH of $C_{10}H_6$). ^{13}C NMR: 14.6 (CH_3), 26.8 (2 CMe_3), 42.4 (2 CMe$_3$), 62.5 (2 CH_2O), 121.6 (2 CH), 124.8 (2 CH), 127.2 (2 CH), 127.7 (2 CH), 130.8 (2 C),, 132.1 (2 C), 140.9 (2 C−N), 164.4, 165.3, 165.5 (2 C=O, C=N), 192.1 (C=O). EI-MS: 692 (1, M^+), 648 (13), 635 (8), 550 (23), 364 (17), 85 (42), 57 (100), 41 (30). Anal. calc. for $C_{34}H_{36}N_4O_8S_2$ (692.79): C 58.94, H 5.24, N 8.09%; found: C 58.61, H 5.14, N 8.18%.

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