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Efficient Synthesis of Highly Functionalized Thiazolidine-4-ones Under Solvent-Free Conditions

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Summary. 4-Phenylthiosemicarbazide reacts smoothly with dimethyl acetylenedicarboxylate in the presence of aldehydes or ketones under solvent free conditions to produce highly functionalized thiazolidine-4-ones.

Keywords. Thiazolidine-4-one; 4-Phenylthiosemicarbazide; Heterocycle synthesis; Solvent-free synthesis.

Introduction

The development of simple synthesis routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. Compounds containing the thiazolidine-4-one ring system are known to possess pharmacological properties such as, analgesics, antibacterial, anticonvulsant, antiparasitic, anti-inflammatory, and herbicidal agents [1–8]. Also some derivatives of thiazolidine-4-one are potent anti-HIV agents [9]. In view of the various physiological activities of thiazolidinones, several approaches for their synthesis have been described [10–12].

As part of our current studies on the development of new routes in heterocycle synthesis [13], we report a one-pot, solvent free synthesis, of highly functionalized thiazolidine-4-ones **4** using 4-phenylthiosemicarbazide (**1**) and dimethyl acetylenedicarboxylate (**2**, *DMAD*) in the presence of aldehydes **3a**–**3f** or ketones **3g**–**3h** (Scheme 1).

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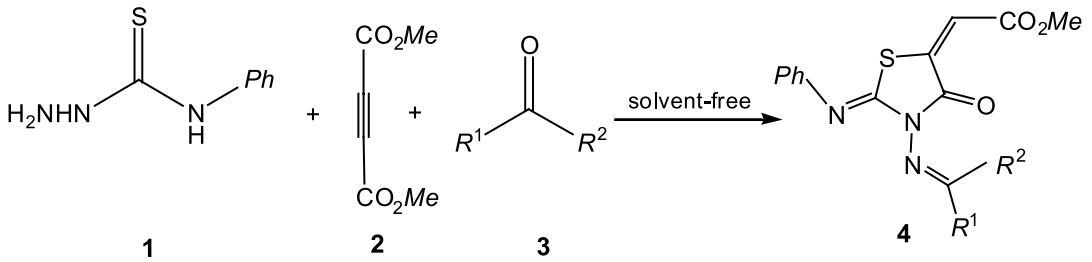
Results and Discussion

The reactions proceeded spontaneously without solvent, and were completed within 8 h. The structures of compounds **4a**–**4h** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectral data. The ^{1}H NMR spectrum of **4a** exhibited three singlets identified as methoxy ($\delta = 3.83$ ppm), olefinic ($\delta = 7.02$ ppm), and imine ($\delta = 9.21$ ppm) protons, along with a multiplet for the aromatic moieties. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **4h** are consistent with the presence of two geometrical isomers in 3:1 ratio. Interconversion between these isomers is slow on the NMR time scale at 370 K.

Unambiguous evidence for the structure of **4a** was obtained from a single-crystal X-ray analysis. An ORTEP [14] diagram of **4a** is shown in Fig. 1. There are 4 molecules of **4a** in the unit cell. The phenyl group is forced out of the plane of the heterocyclic ring and it is twisted by about 6°.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of 1,5-dipolar intermediate **5** from **1** and *DMAD*, which is converted to **6** by proton transfer. Intermediate **6** undergoes cyclization by loss of *Me*OH to produce compound **7**. Condensation of the NH_2 group of **7** with the car-



3, 4	R^1	R^2	Yield / %
a	*Ph*	H	83
b	4-*Me*C_6H_4	H	75
c	4-*Me*OC_6H_4	H	80
d	4-$NO_2C_6H_4$	H	78
e	3-$NO_2C_6H_4$	H	76
f	3-BrC_6H_4	H	70
g	*Me*	*Me*	82
h	*Et*	*Me*	79

Scheme 1

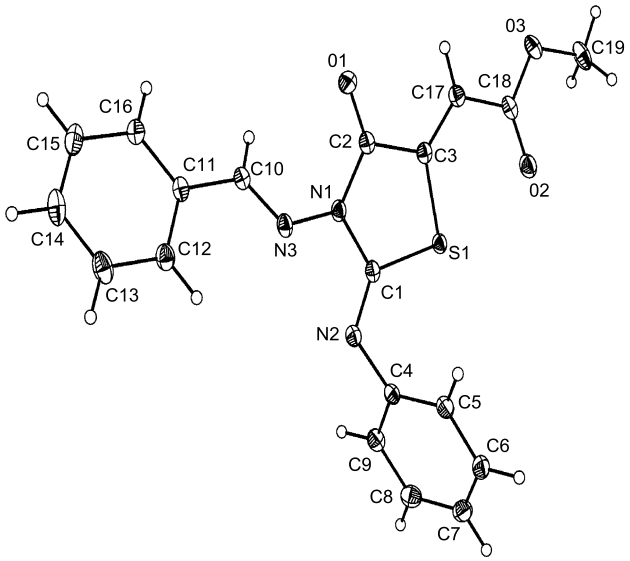


Fig. 1. X-Ray crystal structure of **4a**

bonyl compound **3** leads to thiazolidine-4-one derivatives **4a**–**4h**.

In conclusion, we described a convenient solvent-free route to thiazolidine-4-one derivatives from 4-phenylthiosemicarbazide, *DMAD*, and aldehydes or ketones. These products may be considered as potentially useful synthesis intermediates because they possess atoms with different oxidation states. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials.

Experimental

Compounds **1**–**3** were obtained from Fluka and were used without further purification. Mp Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer. Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer; the results were found to be in good agreement with the calculated values.

General Procedure for the Preparation of Compounds ***4***

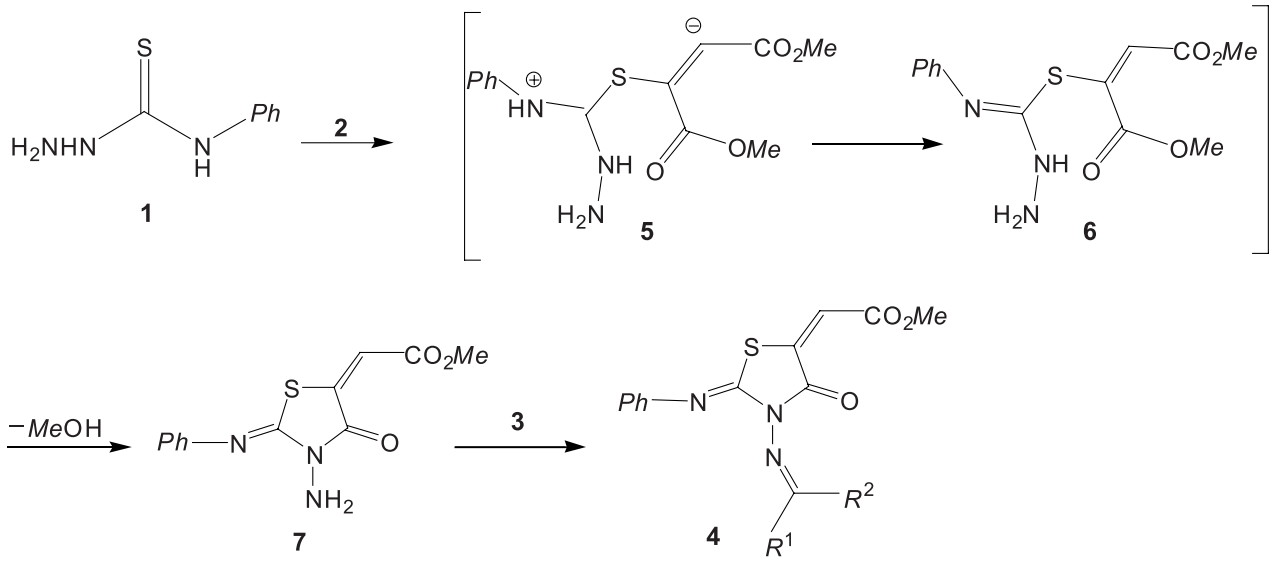
To a mixture of 0.167 g 4-phenylthiosemicarbazide (1 mmol) and 1 mmol of a ketone or an aldehyde, 0.142 g *DMAD* (1 mmol) was added at room temperature. The reaction mixture was then stirred for 8 h. The product was recrystallized from *n*-hexane/*Et*O*Ac* (1/6) mixture.

Methyl 2-[4-oxo-2-(phenylimino)-3-[[(E)-1-phenylmethylidene]amino]-1,3-thiazolan-5-yliden]acetate (**4a**, $C_{19}H_{15}N_3O_3S$)

Yellow powder, yield 0.30 g (83%), mp 170–174°C; IR (KBr): $\bar{\nu} = 1703$ and 1637 (2C=O), 1635, 1317, 1197 cm^{-1}; EI-MS: m/z (%) = 365 (M^+, 2), 261 (98), 103 (30), 77 (66), 59 (100); ^{1}H NMR: $\delta = 3.83$ (s, O*Me*), 7.02 (s, CH), 7.04 (d, $^3J = 9.2$ Hz, 2CH), 7.21 (t, $^3J = 7.4$ Hz, CH), 7.39 (t, $^3J = 7.7$ Hz, 2CH), 7.46–7.57 (m, 3CH), 7.94 (d, $^3J = 7.4$ Hz, 2CH), 9.21 (s, CH) ppm; ^{13}C NMR: $\delta = 53.0$ (O*Me*), 117.4 (CH), 121.4 (2CH), 125.9 (CH), 129.3 (2CH), 129.5 (2CH), 129.8 (2CH), 133.0 (CH), 133.1 (C), 140.0 (C), 147.7 (C), 149.1 (C=N), 161.4 (C=O), 165.7 (HC=N), 166.7 (C=O) ppm.

X-Ray Crystal-Structure of ***4a***

Structure-determination and refinement of data: formula ($C_{19}H_{15}N_3O_3S$): $F_w = 365.40$, monoclinic, space group



Scheme 2

$P2_1/c$, $Z = 4$, $a = 11.3968$ (7) Å, $b = 7.5180$ (5) Å, $c = 20.9847$ (13) Å, $\alpha = 90°$, $\beta = 102.847$ (5)°, $\gamma = 90°$, $V = 1753.02$ (19) Å^3, $D_{calcd} = 1.384\,g\,cm^{-3}$, $R = 0.0335$, $R_w = 0.0869$ (for 4548 reflections), $-15 \leq h \leq 16$; $-10 \leq k \leq 10$; $-29 \leq l \leq 29°$; Mo ($\lambda = 0.71073$ Å), $T = 100.0$ (2) K. The crystallographic data of **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-647816. Copies of the data can be obtained free of charge (http://www.ccdc.cam.ac.uk/data_request/cif, e-mail: data_request@ccdc.cam.ac.uk, or fax: +44-1223-336033).

Methyl 2-[3-[[(E)-1-(4-methylphenyl)methylidene]amino]-4-oxo-2-(phenylimino)-1,3-thiazolan-5-ylidene]acetate
(**4b**, $C_{20}H_{17}N_3O_3S$)
Yellow powder, yield 0.28 g (75%), mp 105–107°C; IR (KBr): $\bar{\nu} = 1726$, 1697 (2C=O), 1634, 1603, 1316, 1197 cm^{-1}; EI-MS: m/z (%) = 379 (M^+, 2), 364 (50), 261 (96), 118 (38), 77 (64), 59 (100); ^{1}H NMR: $\delta = 2.41$ (s, *Me*), 3.81 (s, O*Me*), 6.99 (s, CH), 7.02 (d, $^3J = 7.6$ Hz, 2CH), 7.18 (t, $^3J = 7.2$ Hz, CH), 7.26 (d, $^3J = 7.2$ Hz, 2CH), 7.36 (t, $^3J = 7.1$ Hz, 2CH), 7.80 (d, $^3J = 7.7$ Hz, 2CH), 9.10 (s, CH) ppm; ^{13}C NMR: $\delta = 21.7$ (*Me*), 52.5 (O*Me*), 116.9 (CH), 121.0 (2CH), 125.4 (CH), 129.1 (2CH), 129.3 (2CH), 129.6 (2CH), 139.7 (C), 143.3 (C), 147.3 (C), 148.7 (C), 148.7 (C=N), 161.0 (C=O), 165.7 (HC=N), 166.2 (C=O) ppm.

Methyl 2-[3-[[(E)-1-(4-methyloxyphenyl)methylidene]-amino]-4-oxo-2-(phenylimino)-1,3-thiazolan-5-ylidene]acetate (**4c**, $C_{20}H_{17}N_3O_4S$)
Yellow powder, yield 0.32 g (80%), mp 157–160°C; IR (KBr): $\bar{\nu} = 1725$, 1693 (2C=O), 1634, 1603, 1315, 1232, 1197, 1165 cm^{-1}; EI-MS: m/z (%) = 395 (M^+, 4), 364 (48), 261 (98), 134 (42), 77 (62), 59 (100); ^{1}H NMR: $\delta = 3.81$ (s, O*Me*), 3.87 (s, O*Me*), 6.96 (d, $^3J = 9.0$ Hz, 2CH), 6.99 (s, CH), 7.02 (d, $^3J = 7.4$ Hz, 2CH), 7.18 (t, $^3J = 7.4$ Hz, CH), 7.36 (t, $^3J = 7.6$ Hz, 2CH), 7.87 (d, $^3J = 9.0$ Hz, 2CH), 9.01 (s, CH) ppm; ^{13}C NMR: $\delta = 52.5$ (O*Me*), 55.5 (O*Me*), 114.3 (2CH), 116. 8 (CH), 121.0 (2CH), 125.3 (CH), 128.8 (C), 129.3 (2CH), 131.0 (2CH), 139.8 (C), 147.4 (C), 148.7 (C), 161.0 (C=N), 163.3 (C=O), 165.6 (HC=N), 166.2 (C=O) ppm.

Methyl 2-[3-[[(E)-1-(4-nitrophenyl)methylidene]amino]-4-oxo-2-(phenylimino)-1,3-thiazolan-5-ylidene]acetate
(**4d**, $C_{19}H_{14}N_4O_5S$)
Yellow powder, yield 0.32 g (78%), mp 218–221°C; IR (KBr): $\bar{\nu} = 1740$ and 1712 (2C=O), 1685, 1630, 1600, 1506, 1339, 1297, 1199 cm^{-1}; EI-MS: m/z (%) = 410 (M^+, 2), 364 (40), 261 (94), 149 (36), 77 (62), 59 (100), 46 (52); ^{1}H NMR: $\delta = 3.87$ (s, O*Me*), 7.06 (d, $^3J = 7.7$ Hz, 2CH), 7.08 (s, CH), 7.27 (t, $^3J = 7.5$ Hz, CH), 7.44 (t, $^3J = 7.8$ Hz, 2CH), 8.15 (d, $^3J = 8.7$ Hz, 2CH), 8.37 (d, $^3J = 8.7$ Hz, 2CH), 9.68 (s, CH) ppm; ^{13}C NMR: $\delta = 53.1$ (O*Me*), 118.1 (CH), 121.2 (2CH), 124.5 (2CH), 126.1 (CH), 129.9 (2CH), 130.0 (2CH), 139.2 (C), 139.3 (C), 147.4 (C), 149.1 (C), 150.2 (C=N), 160.0 (HC=N), 161.5 (C=O), 166.6 (C=O) ppm.

Methyl 2-[3-[[(E)-1-(3-nitrophenyl)methylidene]amino]-4-oxo-2-(phenylimino)-1,3-thiazolan-5-ylidene]acetate
(**4e**, $C_{19}H_{14}N_4O_5S$)
Yellow powder, yield 0.31 g (76%), mp 178–179°C; IR (KBr): $\bar{\nu} = 1735$, 1682 (2C=O), 1634, 1513, 1326, 1287, 1204 cm^{-1}; EI-MS: m/z (%) = 410 (M^+, 2), 364 (42), 261 (92), 149 (38), 77 (60), 59 (100), 46 (56); ^{1}H NMR: $\delta = 3.87$ (s, O*Me*), 7.06 (d, $^3J = 7.1$ Hz, 2CH), 7.07 (s, CH), 7.25 (t, $^3J = 7.2$ Hz, CH), 7.43 (t, $^3J = 7.5$ Hz, 2CH), 7.71 (t, $^3J = 7.8$ Hz, CH), 8.34 (d, $^3J = 7.4$ Hz, CH), 8.40 (d, $^3J = 8.1$ Hz, CH), 8.75 (s, CH), 9.59 (s, CH) ppm; ^{13}C NMR: $\delta = 53.1$ (O*Me*), 118.0 (CH), 121.2 (2CH), 124.3 (CH), 126.1 (CH), 126.9 (CH), 129.9 (2CH),

130.4 (CH), 134.4 (CH), 135.2 (C), 139.4 (C), 147.4 (C), 149.1 (C), 160.9 (HC=N), 161.4 (C=N), 166.5 (C=O), 166.6 (C=O) ppm.

Methyl 2-[3-[[(E)-1-(3-bromophenyl)methylidene]amino]-4-oxo-2-(phenylimino)-1,3-thiazolan-5-ylidene]acetate
(**4f**, $C_{19}H_{14}BrN_3O_3S$)
Yellow powder; yield 0.31 g (70%), mp 173–175°C; IR (KBr): $\bar{\nu} = 1727$, 1702 (2C=O), 1634, 1602, 1323, 1294, 1200 cm^{-1}; EI-MS: m/z (%) = 446 (M^+, 4), 444 ($M^+ + 2$, 4), 364 (42), 261 (96), 182 (40), 184 (39), 77 (60), 59 (100); ^{1}H NMR: $\delta = 3.82$ (s, O*Me*), 7.01 (s, CH), 7.02 (d, $^3J = 9.5$ Hz, 2CH), 7.20 (t, $^3J = 7.4$ Hz, CH), 7.34 (t, $^3J = 7.9$ Hz, CH), 7.36 (t, $^3J = 7.9$ Hz, 2CH), 7.64 (d, $^3J = 8.7$ Hz, CH), 7.81 (d, $^3J = 7.7$ Hz, CH), 8.11 (s, CH), 9.27 (s, CH) ppm; ^{13}C NMR: $\delta = 52.6$ (O*Me*), 117.2 (CH), 120.9 (2CH), 123.1 (C), 125.5 (CH), 127.8 (CH), 129.4 (2CH), 130.3 (CH), 131.4 (CH), 134.8 (C), 135.2 (CH), 139.3 (C), 147.1 (C), 158.9 (C=N), 161.0 (C=O), 162.5 (HC=N), 166.2 (C=O) ppm.

Methyl 2-[3-[(1-methylethylidene)amino]-4-oxo-2-(phenylimino)-1,3-thiazolan-5-yliden]acetate
(**4g**, $C_{15}H_{15}N_3O_3S$)
Light yellow powder, yield 0.26 g (82%), mp 215–217°C; IR (KBr): $\bar{\nu} = 1710$, 1635 (2C=O), 1575, 1373, 1325, 1236, 1203 cm^{-1}; EI-MS: m/z (%) = 317 (M^+, 8), 85 (86), 77 (40), 56 (100), 41 (94), ^{1}H NMR: $\delta = 1.93$ (s, *Me*), 2.10 (s, *Me*), 3.91 (s, O*Me*), 6.99 (s, CH), 7.44 (d, $^3J = 7.4$ Hz, 2CH), 7.47 (t, $^3J = 7.2$ Hz, CH), 7.54 (t, $^3J = 7.5$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 19.3$ (*Me*), 25.3 (*Me*), 52.9 (O*Me*), 116.4 (CH), 127.9 (2CH), 129.3 (CH), 129.5 (2CH), 134.6 (C), 142.3 (C), 156.8 (C=N), 165.1 (C=N), 166.8 (C=O), 168.7 (C=O) ppm.

Methyl 2-[3-[[(E)-1-methylpropylidene]amino]-4-oxo-2-(phenylimino)-1,3-thiazolan-5-yliden]acetate
(**4h**, $C_{16}H_{17}N_3O_3S$)
Yellow powder, yield 0.26 g (79%), mp 178–180°C; IR (KBr): $\bar{\nu} = 1707$, 1625 (2C=O), 1575, 1375, 1320, 1204 cm^{-1}; EI-MS: m/z (%) = 345 (M^+, 10), 85 (84), 77 (38), 70 (100), 55 (96).

Major isomer (75%): ^{1}H NMR: $\delta = 1.15$ (t, $^3J = 6.8$ Hz, *Me*), 1.87 (s, *Me*), 2.34 (q, $^3J = 7.1$ Hz, CH_2), 3.86 (s, O*Me*), 6.94 (s, CH), 7.39–7.49 (m, 5CH) ppm; ^{13}C NMR: $\delta = 10.6$ (*Me*), 17.4 (*Me*), 31.8 (CH_2), 52.4 (O*Me*), 115.9 (CH), 127.5 (2CH), 128.8 (CH), 129.1 (2CH), 134.2 (C), 142.1 (C), 156.6 (C=N), 164.6 (C=N), 166.4 (C=O), 172.0 (C=O) ppm.

Minor isomer (25%): ^{1}H NMR: $\delta = 0.95$ (t, $^3J = 6.8$ Hz, *Me*), 2.05 (s, *Me*), 2.32 (q, $^3J = 7.1$ Hz, CH_2), 7.26 (s, CH) ppm; ^{13}C NMR: $\delta = 22.4$ (*Me*), 25.7 (*Me*), 116.0 (CH), 127.4 (2CH), 128.7 (CH), 129.0 (2CH), 141.9 (C), 156.4 (C=N), 164.5 (C=N), 166.3 (C=O), 173.0 (C=O) ppm.

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