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NEW DERIVATIVES OF 3-[(4-PHENYL-5-OXO-1,2,4-TRIAZOLIN-1-YL)-METHYL]-4-SUBSTITUTED 1,2,4-TRIAZOLIN-5-ONE

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Abstract- In the reaction of hydrazide of (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)-acetic acid (**1**) with isocyanate the respective semicarbazide derivatives (**2**) were obtained. Further cyclization with 2% NaOH led to the formation of [3-(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-4-substituted 1,2,4-triazolin-5-one (**3**) and (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**4**).

INTRODUCTION

Compounds with 1,2,4-triazole moiety have received considerable attention among medicinal chemists because molecules with these structural features have been found to display a wide range of potent biological activities, such as antidepressant,¹⁻³ antitumor,⁴ antibacterial,^{5,6} antifungal.⁷⁻⁹ Considering the important biological properties of 1,2,4-triazole compounds, several efficient triazole syntheses have been reported.¹⁰⁻¹⁵ One of the methods of preparing of these compounds is the cyclization reaction of acyl derivatives of semicarbazide in alkaline media.¹⁶

Our study began with the preparation of the hydrazide of (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**1**).¹⁷ This compound was converted to the respective semicarbazide derivatives (**2**) and, after the cyclization reaction in alkaline media, a number of new derivatives (**3**) composed of two 1,2,4-triazolin-5-one systems linked through the methylene group were obtained. The cyclization of semicarbazide (**2j**) led to obtain (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**4**).

RESULTS AND DISCUSSION

Hydrazide of (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**1**) is a starting material for synthesis of 1,2,4-triazolin-5-one. It was obtained in the reaction of ethyl (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetate with 80% hydrazine hydrate.¹⁷ New semicarbazide derivatives (**2**) were obtained by the reaction of **1** with isocyanates. The reaction medium was dry ether and the reaction was carried out in ether at room temperature or by heating substrates in the oil bath for 10 h. Semicarbazide (**2**) were subjected to cyclization in 2% solution of sodium hydroxide obtaining suitable, 3-[(4-phenyl-5-oxo-

1,2,4-triazolin-1-yl)methyl]-4-substituted 1,2,4-triazolin-5-one (**3**) and (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**4**). The reactions were performed according to the Scheme 1.

Scheme 1

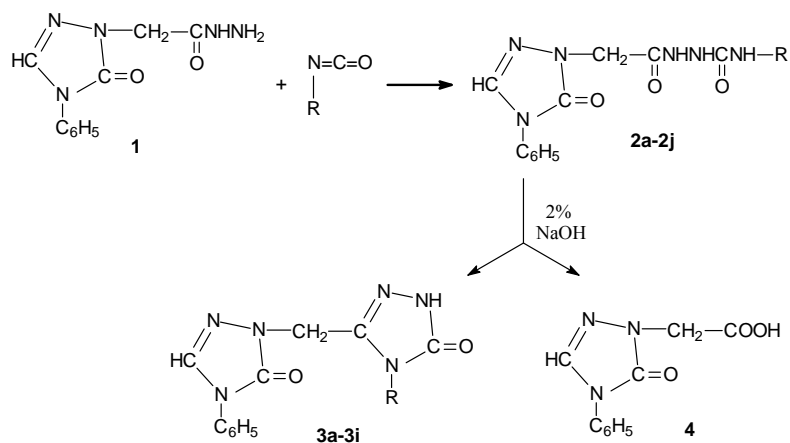


Table 1

Product	Yield	
R	[%]	
2a	C ₄ H ₉	80
2b	4-CH ₃ C ₆ H ₄	82
2c	4-C ₂ H ₅ OC ₆ H ₄	80
2d	4-IC ₆ H ₄	79
2e	4-ClC ₆ H ₄	81
2f	4-CH ₃ OC ₆ H ₄	83
2g	C ₆ H ₅	78
2h	SO ₂ C ₆ H ₅	75
2i	CH ₂ COOC ₂ H ₅	77
2j	COOC ₂ H ₅	74

Table 2

Product	Yield	
R	[%]	
3a	C ₄ H ₉	68
3b	4-CH ₃ C ₆ H ₄	69
3c	4-C ₂ H ₅ OC ₆ H ₄	67
3d	4-IC ₆ H ₄	65
3e	4-ClC ₆ H ₄	66
3f	4-CH ₃ OC ₆ H ₄	63
3g	C ₆ H ₅	62
3h	SO ₂ C ₆ H ₅	58
3i	CH ₂ COOH	62

The reaction outcome depended on the substituents in the starting compounds. In case of semicarbazide derivatives (**2a-2i**) the cyclization led to the formation of 3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-4-substituted 1,2,4-triazolin-5-one (**3a-3i**). The cyclization of semicarbazide (**2i**) was accompanied by hydrolysis of ester group and finally 4-carboxymethyl-3-[(4-phenyl-5-oxo-1,2,4-

triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (**3i**) was obtained. During the reaction cyclization of semicarbazide (**2j**) (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**4**) was formed.

Structure of this compound was confirmed by an independent synthesis. This compound was also obtained during hydrolysis of ethyl (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetate. The IR and ^1H NMR spectra of these compounds were also identical.

Regarding the enol-keto tautomerism, we have established that all cyclization products (**3**) and (**4**) exist in the keto form.

EXPERIMENTAL

Melting points were determined in Fisher-Johns blocs and presented without any corrections. IR spectra were recorded in KBr using Specord IR-75 spectrophotometer. The ^1H NMR spectra were recorded on a Bruker Avance 300 in DMSO- d_6 with TMS as internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance 300 in DMSO- d_6 with TMS as internal standard. Chemicals were purchased from Lancaster or Merck Co. and used without further purification. Purity was checked by TLC on Merck Co. plates Aluminium oxide 60 F₂₅₄ in a $\text{CHCl}_3/\text{C}_2\text{H}_5\text{OH}(10:1)$ solvent system with UV visualization.

1-[(4-Phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]-4-substituted semicarbazide (**2a-2j**)

a) Procedure for **2a-2d**

Hydrazide (2.33g, 0.01 mol) of (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**1**) and isocyanate (0.01 mol) was heated at the 70-110 °C for 10 h. The product was washed with ether to remove the unreacted isocyanate, dried and crystallized from ethanol (79-82%). The results are collected in the Table 1.

4-Butyl-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (**2a**): mp 226-228 °C. IR (cm^{-1}): 3216; 3056; 2967; 1710; 1556; 1448. ^1H NMR δ : 0.88 (t, $J=6.8$ Hz, 3H, CH_3); 1.11-1.80 (m, 4H, 2CH_2); 2.99 (q, $J=6.5$ Hz, 2H, CH_2); 4.49 (s, 2H, CH_2); 7.36-7.82 (m, 5H, arom); 8.53 (s, 1H, CH); 6.38; 9.83; 10.28 (3s, 3H, 3NH). *Anal.* Calcd for $\text{C}_{13}\text{H}_{24}\text{N}_6\text{O}_3$: C 49.98, H 7.74, N 26.90. Found: C 49.92, H 7.68, N 26.93.

1-[(4-Phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]-4-(4-tolyl)semicarbazide (**2b**): mp 254-255 °C.

IR (cm^{-1}): 3244; 3071; 2948; 1723; 1556; 1459. ^1H NMR δ : 2.23 (s, 3H, CH_3); 4.54 (s, 2H, CH_2); 7.05-7.73 (m, 9H, arom); 8.54 (s, 1H, CH); 8.17; 8.59; 10.05 (3s, 3H, 3NH). ^{13}C NMR: 21.2 (CH_3); 47.5 (CH_2); 119.1; 119.7; 122.2; 128.0; 129.9; 130.0; 130.3; 131.4; 131.8 (9x CH_{ar}); 134.9; 136.2; 137.7 (4x C_{ar}); 138.1 (CH); 152.6; 156.1; 167.4 (3x $\text{C}=\text{O}$). *Anal.* Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_6\text{O}_3$: C 55.47, H 6.40, N 24.26. Found: C 55.51, H 6.37, N 24.31.

4-(4-Ethoxyphenyl)-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (**2c**): mp 210-212 °C.

IR (cm^{-1}): 3210; 3068; 2951; 1704; 1549; 1448. ^1H NMR δ : 1.29 (t, $J=5.1$ Hz, 3H, CH_3); 3.96 (q, $J=4.7$ Hz, 2H, CH_2); 4.54 (s, 2H, CH_2); 6.82-7.73 (m, 9H, arom); 8.49 (s, 1H, CH); 7.85; 8.57; 10.03

(3s, 3H, 3NH). *Anal.* Calcd for $C_{17}H_{24}N_6O_4$: C 54.24, H 6.42, N 22.32. Found: C 54.13, H 6.51, N 22.28.

4-(4-Iodophenyl)-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (2d): mp 258-260 °C. IR (cm^{-1}): 3243; 3070; 2923; 1683; 1546; 1484. 1H NMR δ : 4.53 (s, 2H, CH_2); 7.28-7.74 (m, 9H, arom); 8.51(s, 1H, CH); 8.81; 8.92; 10.06 (3s, 3H, 3NH). *Anal.* Calcd for $C_{15}H_{19}N_6O_3I$: C 39.31, H 4.17, N 18.34. Found: C 39.45, H 4.05, N 18.51.

b) Procedure for **2e-2j**

Hydrazide (2.33g, 0.01 mol) of (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (**1**) and isocyanate (0.01 mol) in 10 mL of dry ether was kept for 48 h at rt. Then the formed compound was filtered off, washed with ether and crystallized from ethanol (74-83%). The results are collected in the Table 1.

4-(4-Chlorophenyl)-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (2e): mp 148-150 °C. IR (cm^{-1}): 3248; 3064; 2943; 1691; 1551; 1479. 1H NMR δ : 4.37 (s, 2H, CH_2); 7.32-7.72 (m, 9H, arom); 8.53 (s, 1H, CH); 9.71; 9.90; 10.38 (3s, 3H, 3NH). *Anal.* Calcd for $C_{15}H_{19}N_6O_3Cl$: C 49.11, H 5.22, N 22.91. Found: C 49.08, H 5.20, N 23.02.

4-(4-Methoxyphenyl)-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (2f): mp 236-238 °C. IR (cm^{-1}): 3245; 3073; 2950; 1684; 1558; 1459;. 1H NMR δ : 3.70 (s, 3H, CH_3); 4.53 (s, 2H, CH_2); 6.82-7.84 (m, 9H, arom); 8.57 (s, 1H, CH); 8.54; 8.74; 10.01 (3s, 3H, 3NH). *Anal.* Calcd for $C_{16}H_{22}N_6O_4$: C 53.02, H 6.11, N 23.19. Found: C 53.11, H 6.08, N 23.21.

4-Phenyl-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (2g): mp 248-250 °C. IR (cm^{-1}): 3243; 3071; 2947; 1669; 1556; 1460. 1H NMR δ : 4.57 (s, 2H, CH_2); 6.93-7.72 (m, 10H, arom); 8.55 (s, 1H, CH); 8.23; 8.70; 10.07 (3s, 3H, 3NH). *Anal.* Calcd for $C_{15}H_{20}N_6O_3$: C 54.20, H 6.06, N 25.28. Found: C 54.33, H 6.02, N 25.17.

4-(Benzenesulfonyl)-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (2h): mp 133-135 °C. IR (cm^{-1}): 3248; 3072; 2938; 1672; 1553; 1470. 1H NMR δ : 4.36 (s, 2H, CH_2); 7.35-7.92 (m, 10H, arom); 8.51 (s, 1H, CH); 8.65; 9.30; 9.90 (3s, 3H, 3NH). *Anal.* Calcd for $C_{15}H_{20}N_6O_5S$: C 45.44, H 5.08, N 21.20. Found: C 45.52, H 5.11, N 21.03.

4-Ethoxycarbonylmethyl-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (2i): mp 184-186 °C. IR (cm^{-1}): 3252; 3068; 2941; 1678; 1561; 1484. 1H NMR δ : 1.19 (t, $J=4.7$ Hz, 3H, CH_3); 3.79 (d, $J=5.9$, 2H, CH_2); 4.09 (q, $J=7.1$ Hz, 2H, CH_2); 4.48 (s, 2H, CH_2); 7.35-7.72 (m, 5H, arom); 8.51 (s, 1H, CH); 8.19; 8.51; 9.91 (3s, 3H, 3NH). *Anal.* Calcd for $C_{13}H_{22}N_6O_5$: C 45.60, H 6.47, N 24.55. Found: C 46.72, H 6.39, N 24.46.

4-Ethoxycarbonyl-1-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetyl]semicarbazide (2j): mp 195-197 °C. IR (cm^{-1}): 3250; 3071; 2938; 1681; 1558; 1471. 1H NMR δ : 1.22 (t, $J=4.5$ Hz, 3H, CH_3); 4.14(q, $J=7.1$

Hz, 2H, CH_2); 4.19 (s, 2H, CH_2); 7.36-7.72 (m, 5H, arom); 8.53 (s, 1H, CH); 9.26; 10.33; 10.38 (3s, 3H, 3NH). *Anal.* Calcd for $\text{C}_{12}\text{H}_{20}\text{N}_6\text{O}_5$: C 43.89, H 6.12,

N 25.59. Found: C 43.91, H 6.09, N 25.49.

3-[(4-Phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-4-substituted 1,2,4-triazolin-5-one (3a-3i)

General procedure:

0.01 Mol of semicarbazide (**2a-2i**) dissolved in 40-50 mL (20-25 mmol) of 2% solution of sodium hydroxide was refluxed for 2-10 h (2 h for **2a-2c**, **2e**, **2g**; 4 h for **2h** and 10 h for **2d**, **2f**, **2i**). After cooling, the solution was neutralized with 10% hydrochloric acid. The precipitate was filtered off and recrystallized from ethanol (58-68%). The results are collected in Table 2.

4-Butyl-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3a): mp 98-100 °C. IR (cm^{-1}): 3097; 2966; 1723; 1583; 1507; 1420. ^1H NMR δ : 0.80 (t, $J=7.2$ Hz, 3H, CH_3); 1.14-1.26 (m, 2H, CH_2); 1.32-1.42 (m, 2H, CH_2); 3.55 (t, $J=7.4$ Hz, 2H, CH_2); 4.93 (s, 2H, CH_2); 7.37-7.72 (m, 5H, arom); 8.58 (s, 1H, CH); 11.72 (s, 1H, NH). *Anal.* Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_6\text{O}_2$: C 57.31, H 5.77, N 26.73. Found: C 57.42, H 5.68, N 26.79.

3-[(4-Phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-4-(4-tolyl)-1,2,4-triazolin-5-one (3b): mp 227-229 °C. IR (cm^{-1}): 3048; 2946; 1734; 1592 ; 1505; 1423. ^1H NMR δ : 2.22 (s, 3H, CH_3); 4.87 (s, 2H, CH_2); 7.09-7.70 (m, 9H, arom); 8.30 (s, 1H, CH); 11.91 (s, 1H, NH). ^{13}C NMR: 20.6(CH_3); 40.8 (CH_2); 121.4; 126.6; 127.1; 129.3; 129.5; 129.6 (9x CH_{ar}); 135.5 (CH); 133.5; 138.2; 142.5(4x C_{ar}); 150.5; 154.4 (2x $\text{C}=\text{O}$). *Anal.* Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_6\text{O}_2$: C 62.05, H 4.62, N 24.12. Found: C 62.13, H 4.54, N 24.18.

4-(4-Ethoxyphenyl)-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3c): mp 140-142 °C. IR (cm^{-1}): 3065; 2956; 1728; 1589; 1510; 1431. ^1H NMR δ : 1.28 (t, $J=6.9$ Hz, 3H, CH_3); 3.89 (q, $J=6.9$ Hz, 2H, CH_2); 4.84 (s, 2H, CH_2); 6.85-7.50 (m, 9H, arom); 8.36 (s, 1H, CH); 11.89 (s, 1H, NH). *Anal.* Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_6\text{O}_2$: C 60.30, H 4.79, N 22.21. Found: C 60.41, H 4.81, N 22.09.

4-(4-Iodophenyl)-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3d): mp 252-254 °C. IR (cm^{-1}): 3097; 2952; 1728; 1588; 1506, 1434. ^1H NMR δ : 4.91 (s, 2H, CH_2); 7.11-7.77 (m, 9H, arom); 8.34 (s, 1H, CH); 12.03 (s, 1H, NH). *Anal.* Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_6\text{O}_2\text{I}$: C 44.36, H 2.84, N 18.26. Found: C 44.26, H 2.91, N 18.32.

4-(4-Chlorophenyl)-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3e): mp 157-159 °C. IR (cm^{-1}): 3088; 2947; 1725; 1579; 1509; 1432. ^1H NMR δ : 5.02 (s, 2H, CH_2); 7.32-7.63 (m, 9H, arom); 8.36 (s, 1H, CH); 14.03 (s, 1H, NH). ^{13}C NMR: 39.9 (CH_2); 121.6; 127.3; 129.3; 129.4; 131.7; 133.4; 134.3 (9x CH_{ar}); 135.9(CH); 131.7; 133.4; 134.3; 147.5 (4x C_{ar}); 150.31; 68.6 (2x $\text{C}=\text{O}$). *Anal.* Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_6\text{O}_2\text{Cl}$: C 55.36, H 3.55, N 22.79. Found: C 55.42, H 3.61, N 22.64.

4-(4-Methoxyphenyl)-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3f):

mp 235-236 °C. IR (cm⁻¹): 3095; 2952; 1728; 1589; 1505; 1438. ¹H NMR δ: 3.66 (s, 3H, CH₃); 4.84 (s, 2H, CH₂); 6.89-7.51 (m, 9H, arom); 8.36 (s, 1H, CH); 11.89 (s, 1H, NH). *Anal.* Calcd for C₁₈H₁₆N₆O₃: C 59.33, H 4.42, N 23.06. Found: C 59.44, H 4.51, N 23.17.

4-Phenyl-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3g): mp 183-185 °C. IR (cm⁻¹): 3094; 2948; 1731; 1598; 1503; 1432. ¹H NMR δ: 4.89 (s, 2H, CH₂); 6.95-7.68 (m, 10H, arom); 8.31 (s, 1H, CH); 11.99 (s, 1H, NH). *Anal.* Calcd for C₁₇H₁₄N₆O₂: C 61.06, H 4.22, N 25.13. Found: C 60.08, H 4.31, N 25.21.

4-Benzenesulfonyl-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3h): mp 106 - 108 °C. IR (cm⁻¹): 3092; 2938; 1723; 1588; 1507; 1440. ¹H NMR δ: 4.55 (s, 2H, CH₂); 7.12-7.86 (m, 10H, arom); 8.49 (s, 1H, CH); 12.07 (s, 1H, NH). *Anal.* Calcd for C₁₇H₁₄N₆O₄S: C 51.24, H 3.54, N 21.09. Found: C 51.33, H 3.32, N 21.21.

4-Carboxymethyl-3-[(4-phenyl-5-oxo-1,2,4-triazolin-1-yl)methyl]-1,2,4-triazolin-5-one (3i): mp 150-151 °C. IR (cm⁻¹): 3089; 2942; 1722; 1586; 1509; 1438. ¹H NMR δ: 3.44 (s, 1H, OH); 4.42 (s, 2H, CH₂); 4.91 (s, 2H, CH₂); 7.37-7.67 (m, 5H, arom); 8.50 (s, 1H, CH); 11.83 (s, 1H, NH). *Anal.* Calcd for C₁₃H₁₂N₆O₄: C 49.36, H 3.82, N 26.57. Found: C 49.48, H 3.89, N 26.49.

1-(4-Phenyl-5-oxo-1,2,4-triazolin-1-yl)acetic acid (4)

Method A

Semicarbazide (**2j**) (3.28g, 0.01 mol) dissolved in 40-50 mL (20-25 mmol) of 2% solution of sodium hydroxide was refluxed for 2 h. After cooling, the solution was neutralized with 10% hydrochloric acid. The precipitate was filtered off and recrystallized from ethanol (85%).

Method B

Ethyl (4-phenyl-5-oxo-1,2,4-triazolin-1-yl)acetate (2.47g, 0.01 mol) and 10 mL (30 mmol) 3M hydrochloric acid was refluxed for 2 h. After cooling the product was filtered off and recrystallized from ethanol (85%).

mp 147-149 °C. IR (cm⁻¹): 3091; 2958; 1721; 1554; 1512; 1443. ¹H NMR δ: 4.56 (s, 2H, CH₂); 7.35-7.70 (m, 5H, arom); 8.34 (s, 1H, CH); 11.97 (s, 1H, OH). *Anal.* Calcd for C₁₀H₉N₃O₃: C 54.79, H 4.13, N 19.17. Found: C 54.68, H 4.20, N 19.24.

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