HETEROCYCLES, Vol. 68, No. 4, 2006, pp. 779 - 785. © The Japan Institute of Heterocyclic Chemistry
Received, 12th December, 2005, Accepted, 28th February, 2006, Published online, 3rd March, 2006. COM-05-10649

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

Monika Wujec, Monika Pitucha, and Maria Dobosz*

Department of Organic Chemistry, Medical University, 6 Staszica Str., 20-081 Lublin, Poland, monika.wujec@am.lublin.pl

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

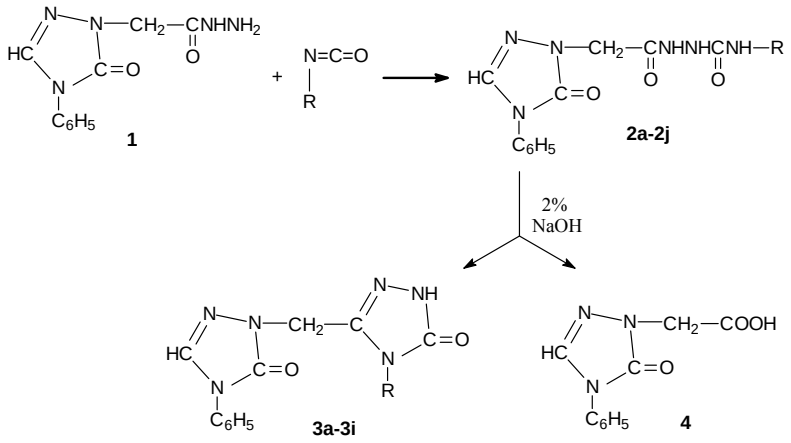

Table 1

Product		Yield
	R	[%]
2a	C_4H_9	80
2b	4-$CH_3C_6H_4$	82
2c	4-$C_2H_5OC_6H_4$	80
2d	4-IC_6H_4	79
2e	4-ClC_6H_4	81
2f	4-$CH_3OC_6H_4$	83
2g	C_6H_5	78
2h	$SO_2C_6H_5$	75
2i	$CH_2COOC_2H_5$	77
2j	$COOC_2H_5$	74

Table 2

Product		Yield
	R	[%]
3a	C_4H_9	68
3b	4-$CH_3C_6H_4$	69
3c	4-$C_2H_5OC_6H_4$	67
3d	4-IC_6H_4	65
3e	4-ClC_6H_4	66
3f	4-$CH_3OC_6H_4$	63
3g	C_6H_5	62
3h	$SO_2C_6H_5$	58
3i	CH_2COOH	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 ^{1}H 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 ^{1}H NMR spectra were recorded on a Brucker Avance 300 in DMSO-d_6 with TMS as internal standard. The ^{13}C NMR spectra were recorded on a Brucker 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 F_{254} in a $CHCl_3/C_2H_5OH$(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 ºC 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 ºC. IR (cm^{-1}): 3216; 3056; 2967; 1710; 1556; 1448. ^{1}H NMR δ: 0.88 (t, *J*=6.8 Hz, 3H, C**H**$_3$); 1.11-1.80 (m, 4H, 2C**H**$_2$); 2.99 (q, *J*=6.5 Hz, 2H, C**H**$_2$); 4.49 (s, 2H, C**H**$_2$); 7.36-7.82 (m, 5H, arom); 8.53 (s, 1H, C**H**); 6.38; 9.83; 10.28 (3s, 3H, 3N**H**). *Anal.* Calcd for $C_{13}H_{24}N_6O_3$: 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 ºC.

IR (cm^{-1}): 3244; 3071; 2948; 1723; 1556; 1459. ^{1}H NMR δ: 2.23 (s, 3H, C**H**$_3$); 4.54 (s, 2H, C**H**$_2$); 7.05-7.73 (m, 9H, arom); 8.54 (s, 1H, C**H**); 8.17; 8.59; 10.05 (3s, 3H, 3N**H**). ^{13}C NMR: 21.2 (**C**H$_3$); 47.5 (**C**H$_2$); 119.1; 119.7; 122.2; 128.0; 129.9; 130.0; 130.3; 131.4; 131.8 (9x**C**H$_{ar}$); 134.9; 136.2; 137.7 (4x **C**$_{ar}$); 138.1 (**C**H); 152.6; 156.1; 167.4 (3x **C**=O). *Anal.* Calcd for $C_{16}H_{22}N_6O_3$: 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 ºC. IR (cm^{-1}): 3210; 3068; 2951; 1704; 1549; 1448. ^{1}H NMR δ: 1.29 (t, *J*=5.1 Hz, 3H, C**H**$_3$); 3.96 (q, *J*=4.7Hz, 2H, C**H**$_2$); 4.54 (s, 2H, C**H**$_2$); 6.82-7.73 (m, 9H, arom); 8.49 (s, 1H, C**H**); 7.85; 8.57; 10.03

(3s, 3H, 3N**H**). *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 ºC. IR (cm^{-1}): 3243; 3070; 2923; 1683; 1546; 1484. ^{1}H NMR δ: 4.53 (s, 2H, C**H**$_2$); 7.28-7.74 (m, 9H, arom); 8.51(s, 1H, C**H**); 8.81; 8.92; 10.06 (3s, 3H, 3N**H**). *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 ºC. IR (cm^{-1}): 3248; 3064; 2943; 1691; 1551; 1479. ^{1}H NMR δ: 4.37 (s, 2H, C**H**$_2$); 7.32-7.72 (m, 9H, arom); 8.53 (s, 1H, C**H**); 9.71; 9.90; 10.38 (3s, 3H, 3N**H**). *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 ºC. IR (cm^{-1}): 3245; 3073; 2950; 1684; 1558; 1459;. ^{1}H NMR δ: 3.70 (s, 3H, C**H**$_3$); 4.53 (s, 2H, C**H**$_2$); 6.82-7.84 (m, 9H, arom); 8.57 (s, 1H, C**H**); 8.54; 8.74; 10.01 (3s, 3H, 3N**H**). *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 ºC. IR (cm^{-1}): 3243; 3071; 2947; 1669; 1556; 1460. ^{1}H NMR δ: 4.57 (s, 2H, C**H**$_2$); 6.93-7.72 (m, 10H, arom); 8.55 (s, 1H, C**H**); 8.23; 8.70; 10.07 (3s, 3H, 3N**H**). *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 ºC. IR (cm^{-1}): 3248; 3072; 2938; 1672; 1553; 1470. ^{1}H NMR δ: 4.36 (s, 2H, C**H**$_2$); 7.35-7.92 (m, 10H, arom); 8.51 (s, 1H, C**H**); 8.65; 9.30; 9.90 (3s, 3H, 3N**H**). *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 ºC. IR (cm^{-1}): 3252; 3068; 2941; 1678; 1561; 1484. ^{1}H NMR δ: 1.19 (t, *J*=4.7 Hz, 3H, C**H**$_3$); 3.79 (d, *J*=5.9, 2H, C**H**$_2$); 4.09 (q, *J*=7.1 Hz, 2H, C**H**$_2$); 4.48 (s, 2H, C**H**$_2$); 7.35-7.72 (m, 5H, arom); 8.51 (s, 1H, C**H**); 8.19; 8.51; 9.91 (3s, 3H, 3N**H**). *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 ºC. IR (cm^{-1}): 3250; 3071; 2938; 1681; 1558; 1471. ^{1}H NMR δ: 1.22 (t, *J*=4.5 Hz, 3H, C**H**$_3$); 4.14(q, *J*=7.1

Hz, 2H, C**H**$_2$); 4.19 (s, 2H, C**H**$_2$); 7.36-7.72 (m, 5H, arom); 8.53 (s, 1H, C**H**); 9.26; 10.33; 10.38 (3s, 3H, 3N**H**). *Anal.* Calcd for $C_{12}H_{20}N_6O_5$: 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 ºC. IR (cm^{-1}): 3097; 2966; 1723; 1583; 1507; 1420. ^{1}H NMR δ: 0.80 (t, *J*=7.2 Hz, 3H, C**H**$_3$); 1.14-1.26 (m, 2H, C**H**$_2$); 1.32-1.42 (m, 2H, C**H**$_2$); 3.55 (t, *J*=7.4 Hz, 2H, C**H**$_2$); 4.93 (s, 2H, C**H**$_2$); 7.37-7.72 (m, 5H, arom); 8.58 (s, 1H, C**H**); 11.72 (s, 1H, N**H**). *Anal.* Calcd for $C_{15}H_{18}N_6O_2$: 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 ºC. IR (cm^{-1}): 3048; 2946; 1734; 1592 ; 1505; 1423. ^{1}H NMR δ: 2.22 (s, 3H, C**H**$_3$); 4.87 (s, 2H, C**H**$_2$); 7.09-7.70 (m, 9H, arom); 8.30 (s, 1H, C**H**); 11.91 (s, 1H, N**H**). ^{13}C NMR: 20.6(**C**H$_3$); 40.8 (**C**H$_2$); 121.4; 126.6; 127.1; 129.3; 129.5; 129.6 (9x**C**H$_{ar}$); 135.5 (**C**H); 133.5; 138.2; 142.5(4x **C**$_{ar}$); 150.5; 154.4 (2x **C**=O). *Anal.* Calcd for $C_{18}H_{16}N_6O_2$: 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 ºC. IR (cm^{-1}): 3065; 2956; 1728; 1589; 1510; 1431. ^{1}H NMR δ: 1.28 (t, *J*=6.9 Hz, 3H, C**H**$_3$); 3.89 (q, *J*=6.9 Hz, 2H, C**H**$_2$); 4.84 (s, 2H, C**H**$_2$); 6.85-7.50 (m, 9H, arom); 8.36 (s, 1H, C**H**); 11.89 (s, 1H, NH). *Anal.* Calcd for $C_{19}H_{18}N_6O_2$: 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 ºC. IR (cm^{-1}): 3097; 2952; 1728; 1588; 1506, 1434. ^{1}H NMR δ: 4.91 (s, 2H, C**H**$_2$); 7.11-7.77 (m, 9H, arom); 8.34 (s, 1H, C**H**); 12.03 (s, 1H, N**H**). *Anal.* Calcd for $C_{17}H_{13}N_6O_2I$: 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)**: mp157-159 ºC. IR (cm^{-1}): 3088; 2947; 1725; 1579; 1509; 1432. ^{1}H NMR δ: 5.02 (s, 2H, C**H**$_2$); 7.32-7.63 (m, 9H, arom); 8.36 (s, 1H, C**H**); 14.03 (s, 1H, N**H**). ^{13}C NMR: 39.9 (**C**H$_2$); 121.6; 127.3; 129.3; 129.4; 131.7; 133.4; 134.3 (9x**C**H$_{ar}$); 135.9(**C**H); 131.7; 133.4; 134.3; 147.5 (4x **C**$_{ar}$); 150.31; 68.6 (2x **C**=O). *Anal.* Calcd for $C_{17}H_{13}N_6O_2Cl$: 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 ºC. IR (cm^{-1}): 3095; 2952; 1728; 1589; 1505; 1438. ^{1}H NMR δ: 3.66 (s, 3H, C**H**$_3$); 4.84 (s, 2H, C**H**$_2$); 6.89-7.51 (m, 9H, arom); 8.36 (s, 1H, C**H**); 11.89 (s, 1H, N**H**). ***Anal.*** Calcd for $C_{18}H_{16}N_6O_3$: 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 ºC. IR (cm^{-1}): 3094; 2948; 1731; 1598; 1503; 1432. ^{1}H NMR δ: 4.89 (s, 2H, C**H**$_2$); 6.95-7.68 (m, 10H, arom); 8.31 (s, 1H, C**H**); 11.99 (s, 1H, N**H**). ***Anal.*** Calcd for $C_{17}H_{14}N_6O_2$: 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 ºC. IR (cm^{-1}): 3092; 2938; 1723; 1588; 1507; 1440. ^{1}H NMR δ: 4.55 (s, 2H, C**H**$_2$); 7.12-7.86 (m, 10H, arom); 8.49 (s, 1H, C**H**); 12.07(s, 1H, N**H**). ***Anal.*** Calcd for $C_{17}H_{14}N_6O_4S$: 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 ºC. IR (cm^{-1}): 3089; 2942; 1722; 1586; 1509; 1438. ^{1}H NMR δ: 3.44 (s, 1H, O**H**); 4.42 (s, 2H, C**H**$_2$); 4.91 (s, 2H, C**H**$_2$); 7.37-7.67 (m, 5H, arom); 8.50 (s, 1H, C**H**); 11.83 (s, 1H, N**H**). ***Anal.*** Calcd for $C_{13}H_{12}N_6O_4$: 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 ºC. IR (cm^{-1}): 3091; 2958; 1721; 1554; 1512; 1443. ^{1}H NMR δ: 4.56 (s, 2H, C**H**$_2$); 7.35-7.70 (m, 5H, arom); 8.34 (s, 1H, C**H**); 11.97 (s, 1H, O**H**). ***Anal.*** Calcd for $C_{10}H_9N_3O_3$: C 54.79, H 4.13, N 19.17. Found: C 54.68, H 4.20, N 19.24.

REFERENCES

1. D. L. Temple and W. G. Lobeck, US Patent, 4 386,091 (*Chem. Abstr.*, 1983, **99**, 10529).

2. D. L. Temple and W. G. Lobeck, US Patent, 4 487,773 (*Chem. Abstr.*, 1985, **102**, 166780).

3. A. Catanese and E. Lisciari, *Boll. Chim. Farm.*, 1970, **109**, 369.

4. A. A. Ikizler, A. Ikizler, S. Mevlüt, and Y. Nuri, *Acta Polon. Pharm.,* 1996, **54**, 363.

5. A. Demirbas, C. B. Johanson, N. Duman, and A. A. Ikizler, *Acta Polon. Pharm.,* 1996, **53**, 117.

6. H. Yuksek, A. Demirbas, A. Ikizler, C. B. Johansson, C. Celic, and A. A. Ikizler, *Arzneim-Forsch*., 1997, **47**, 405.

7. R. J. Brown, D. A. Frasier, C. Happersett, P. P.Castro, and C. G. Sterrnberg, PCT Patent, 96 26,191 (*Chem. Abstr.,* 1996, **125**, 247833).

8. T. Ohsumi, T. Hirose, K. Ujihara, and R. Matsunaga, PCT Patent, 96 38,425 (*Chem. Abstr.,* 1997, **126**, 104094).

9. A. A. Ikizler, F. Ucaf, H. Yuskek, A. Aytin, J. Yasa, and Y. Gezer, *Acta Polon. Pharm.,* 1997, **54**, 2.

10. G. Mazzone, G. Puglisi, A. Corsaro, A. Panico, F. Bonina, M. Amico-Roxas, A. Caruso, and S. Trombadore, *Eur. J. Med. Chim. Ther*., 1986, **21**, 277.

11. J. Kane, *Synthesis*, 1987, 912.

12. T. Kagawa, M. Kieda, H. Sugano, Y. Yamamoto, and Y. Miyagi, Jpn Patent, 03 106,865 (*Chem. Abstr.,* 1991, **115**, 183319).

13. Daliang Li, Hongli Bao, and Tianpa You, *Heterocycles*, 2005, **65**, 1957.

14. H. Koshima, M. Hamada, M. Tani, S. Iwasaki, and F. Sato, *Heterocycles*, 2002, **57**, 2145.

15. M. Dobosz and M. Wujec, *Heterocycles*, 2002, **57**, 1135.

16. M. Dobosz, M. Pitucha, I. Dybała, and A. E. Kozioł, *Collect. Czech. Chem. Comm.,* 2003, **68**, 792.

17. M. Dobosz and M. Struga, *Acta Polon. Pharm.,* 1997, **57**, 313.