Chemistry of Heterocyclic Compounds, Vol. 46, No. 9, 2010

SYNTHESIS AND STRUCTURE OF SUBSTITUTED TRIAZOLOQUINAZOLINES

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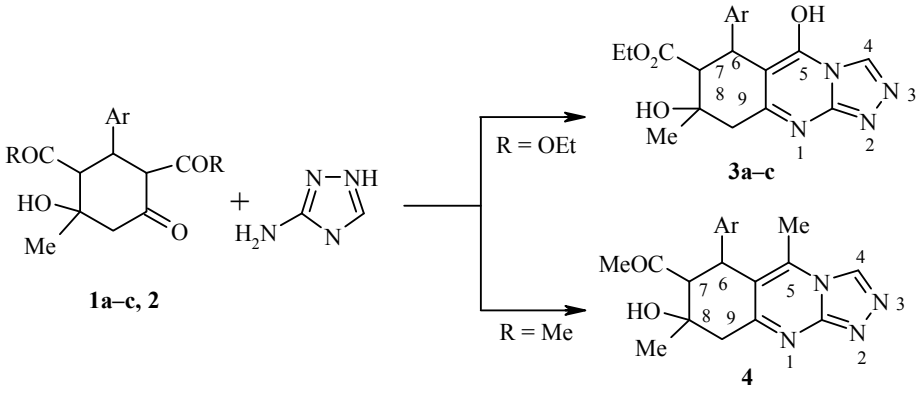
Keywords: 3-amino-1,2,4-triazole, hydroxycyclohexanones, hydroxyoxocyclohexanedicarboxylates, triazoloquinazolines.

Carbonyl-substituted hydroxycyclohexanones such as diethyl 2-Ar-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylates (**1**) and 3-Ar-2,4-diacetyl-5-hydroxy-5-methylcyclohexanones (**2**) are commonly used for the construction of condensed systems containing a five-membered heterocycle [1]. There have been only a few examples of the construction of six-membered heterocycles starting from such reagents.

We have studied the reaction of carbonyl-substituted hydroxycyclohexanones **1a-c** and **2** with 3-amino-1,2,4-triazole. The presence of several nucleophilic sites in the reagent and their arrangement should be conducive for the annelation of a six-membered heterocycle and generation of systems possessing different types of ring fusion and possessing of the nitrogen atoms at different positions.

Heating equimolar amounts of the reagents at 120-140°C without solvent gave previously unreported triazoloquinazolines: ethyl 6-Ar-5,8-dihydroxy-8-methyl-6,7,8,9-tetrahydro[1,2,4]triazolo[3,4-*b*]quinazoline-7-carboxylates **3a-c** and 7-acetyl-6-Ar-8-hydroxy-5,8-dimethyl-6,7,8,9-tetrahydro[1,2,4]triazolo[3,4-*b*]quinazoline (**4**).



1a, 2, 3a, 4 Ar = Ph; **1b**, **3b** Ar = 4-$OMeC_6H_4$, **1c**, **3c** Ar = 3-$NO_2C_6H_4$

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1420-1422, September, 2010. Original article submitted March 25, 2010.

The ^{1}H NMR spectra show a doublet for vicinal protons H-6 and H-7 (J = 10-11 Hz), doublet for geminal protons H-9a and H-9e (J = 17-18 Hz), and signals for the protons of the hydroxyl groups and one ethoxy or acetyl substituent. The 2.27/8.48 ppm/ppm cross-peak in the NOESY spectrum of quinazoline **4** reflects coupling of the protons of the methyl group at C-5 atom with proton H-4 arising only in the case of a linear system and 2,3-arrangement of the nitrogen atoms in the triazole ring. The position for C-5 atom (150 ppm) in the ^{13}C NMR spectrum of ester **3a** indicates that this compound exists as an enol.

These results indicate a new type of fusion of six-membered azaheterocycles to the carbonyl-substituted hydroxycyclohexanones studied in this work.

The ^{1}H NMR, ^{13}C NMR, and NOESY spectra were taken on a Varian 400 spectrometer at 400 MHz in DMSO-d_6 with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with 2:2:1 hexane–ethyl acetate–chloroform as the eluent.

Ethyl 5,8-dihydroxy-8-methyl-6-phenyl-6,7,8,9-tetrahydro[1,2,4]triazolo[3,4-*b*]quinazoline-7-carboxylate (3a). A mixture of oxocyclohexanedicarboxylate **1** (1 g, 3 mmol) and 3-amino-1,2,4-triazole (0.24 g, 3 mmol) was maintained for 20 min at 120-140°C. The crystals formed on cooling were washed with 2-propanol and diisopropyl ether to give 1.00 g (93%) compound **3a** as colorless crystals; mp 274-276°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.02 (3H, t, J = 7.0, C<u>H</u>$_3$CH$_2$O); 1.24 (3H, s, 8-CH$_3$); 2.60 (1H, d, J = 17.0, H-9*e*); 2.68 (1H, d, J = 11.0, H-7); 3.21 (1H, d, J = 17.0, H-9*a*); 3.88-4.03 (2H, m, MeC<u>H</u>$_2$O); 4.28 (1H, d, J = 10.0, H-6); 4.81 (1H, s, 8-OH); 7.09-7.18 (5H, m, C$_6$H$_5$); 8.10 (1H, s, H-4); 13.1 (1H, br. s, 5-OH). ^{13}C NMR spectrum, δ, ppm: 14.5 (OCH$_2$<u>C</u>H$_3$), 27.9 (8-CH$_3$), 41.5 (C-6), 42.1 (C-9), 59.0 (C-7), 60.3 (O<u>C</u>H$_2$Me), 68.6 (C-8), 108 (C-5a), 126, 128, 129, 144 (C$_6$H$_5$), 147 (C-1a), 150 (C-5), 152 (C-4), 155 (C-9a), 172 (C=O). NOESY spectrum, ppm/ppm: 1.24/2.60 (8-CH$_3$/H-9*e*); 1.24/2.68 (H-9*a*/H-7); 1.24/3.21 (8-CH$_3$/H-9*a*); 1.24/4.81 (8-CH$_3$/8-OH); 2.60/4.81 (H-9*e*/8-OH); 2.68/7.10 (H-7/*ortho*-C$_6$H$_5$); 2.68/3.21 (H-7, H-9*a*); 4.28/7.10 (H-6/*ortho*-C$_6$H$_5$). Found, %: C 62.23; H 5.84; N 15.27. $C_{19}H_{20}N_4O_4$. Calculated, %: C 61.95; H, 5.47; N 15.21.

Ethyl 5,8-dihydroxy-6-(4-methoxyphenyl)-8-methyl-6,7,8,9-tetrahydro[1,2,4]triazolo[3,4-*b*]quinazoline-7-carboxylate (3b) was synthesized in 72% yield as colorless crystals analogously to compound **3a**; mp 269-271°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.10 (3H, t, J = 7.2, C<u>H</u>$_3$CH$_2$O); 1.41 (3H, s, 8-CH$_3$); 2.73 (1H, d, J = 10.0, H-7); 2.87 (1H, d, J = 17.0, H-9*e*); 3.21 (1H, d, J = 17.0, H-9*a*); 3.74 (1H, s, 8-OH); 3.76 (3H, s, OCH$_3$); 4.11 (2H, quin. d, J = 7.1, J = 2.3, MeC<u>H</u>$_2$O); (1H, d, J = 10.0, H-6); 6.80, 7.07 (4H, two d, J = 8.4, 4-OMeC$_6$<u>H</u>$_4$); 8.01 (1H, s, H-4). Found, %: C 59.84; H 5.97; N 13.16. $C_{20}H_{22}N_4O_5$. Calculated, %: C 60.29; H 5.57; N 14.06.

Ethyl 5,8-dihydroxy-8-methyl-6-(3-nitrophenyl)-6,7,8,9-tetrahydro[1,2,4]triazolo[3,4-*b*]quinazoline-7-carboxylate (3c) was synthesized in 81% yield as colorless crystals analogously to compound **3a**; mp 265-267°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.99 (3H, t, J = 7.0 C<u>H</u>$_3$CH$_2$O); 1.27 (3H, s, 8-CH$_3$); 3.63 (1H, d, J = 17.0, H-9*e*); 2.80 (1H, d, J = 11.0, H-7); 3.30 (1H, d, J = 17.0, H-9*a*); 3.89-4.02 (2H, m, MeC<u>H</u>$_2$O); 4.41 (1H, J = 10.0, H-6); 4.95 (1H, s, 8-OH); 7.50, 7.62, 7.96, 8.01 (4H, t, d, s, d, J = 8.0, J = 7.2, J = 8.0, 3-NO$_2$C$_6$H$_4$); 8.13 (1H, s, H-4); 13.3 (1H, br. s, 5-OH). Found, %: C 55.11; H 4.86; N 16.34. $C_{19}H_{19}N_5O_6$. Calculated, %: C 55.20; H 4.63; N 16.94.

7-Acetyl-8-hydroxy-5,8-dimethyl-6-phenyl-6,7,8,9-tetrahydro[1,2,4]triazolo[3,4-*b*]quinazoline (4) was synthesized in 25% yield as colorless crystals analogously to compound **3a**; mp 223-224°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.27 (3H, s, 8-CH$_3$); 2.10 (3H, s, 7-CH$_3$–C(O)); 2.23 (3H, s, 5-CH$_3$); 2.94 (1H, d, J = 17.0, H-9*e*); 3.05 (1H, d, J = 10.0, H-7); 3.39 (1H, d, J = 10.0, H-9*a*); 4.75 (1H, d, J = 10.0, H-6); 4.89 (1H, s, 8-OH); 7.08-7.26 (5H, m, C$_6$H$_5$); 8.48 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 15.5 (5-CH$_3$), 28.0 (8-CH$_3$), 31.9 (7-<u>C</u>H$_3$C(O)), 42.8 (C-6), 49.1 (C-9), 66.3 (C-7), 69.3 (C-8), 121 (C-5a), 127, 128, 129, 145 (C$_6$H$_5$), 146 (C-1a), 153 (C-9a), 156 (C-4), 164 (C-5), 210 (C=O). NOESY spectrum, ppm/ppm: 1.27/2.10 (5-CH$_3$/7-CH$_3$C(O)); 1.27/2.94 (8-CH$_3$/H-9*e*); 1.27/3.05 (8-CH$_3$/H-7); 1.27/3.39 (8-CH$_3$,/H-9*a*), 1.27/4.89 (8-CH$_3$/8-OH); 2.10/3.05 (7CH$_3$C(O)/H-7); 2.10/4.75 (7-CH$_3$C(O)/H-6); 2.10/7.10 (7-CH$_3$C(O)/*ortho*-C$_6$H$_5$);

2.23/4.75 (5-CH_3/H-6); 2.23/7.10 (8-CH_3/*ortho*-C_6H_5); 2.23/8.48 (5-CH_3/H-4); 2.94/4.89 (H-9*e*/OH), 3.05/3.39 (H-9*a*/H-7,); 3.05/7.10 (H-7/*ortho*-C_6H_5); 4.75/7.10 (H-6/*ortho*-C_6H_5). Found, %: C 67.73; H 6.21; N 16.64. $C_{19}H_{20}N_4O_2$. Calculated, %: C 67.84; H 5.99; N 16.66.

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