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LETTERS TO THE EDITOR

Ketoalkylation of 2,4-Dihydro-3*H*-1,2,4-triazol-3-one in Dimethylsulfoxide

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Triazolone derivatives are organic compounds having a wide spectrum of biological activity [1–10]. Therefore, functionalization of triazolone ring is one of the major directions for designing compounds with a specific type of biological action.

Most known methods for the synthesis of functional derivatives of triazolone involve its alkylation with methyl iodide [2, 7], dimethyl sulfate [11], ethyl bromoacetate [3–5, 9], dibutyl dicarbonate [13], benzoyl chloride [7], bromoacetophenone [12] in the presence of solid bases or under refluxing with equimolar amount of metallic Na. The authors have shown that the degree of alkylation of triazolone derivatives can be adjusted by varying the ratio of the reactants, and the direction of the process, by changing in pH and solvation properties of the medium [11]. Alkylation of 2,4-dihydro-3*H*-1,2,4-triazol-3-one and its derivatives with α-iodoketones previously was not investigated.

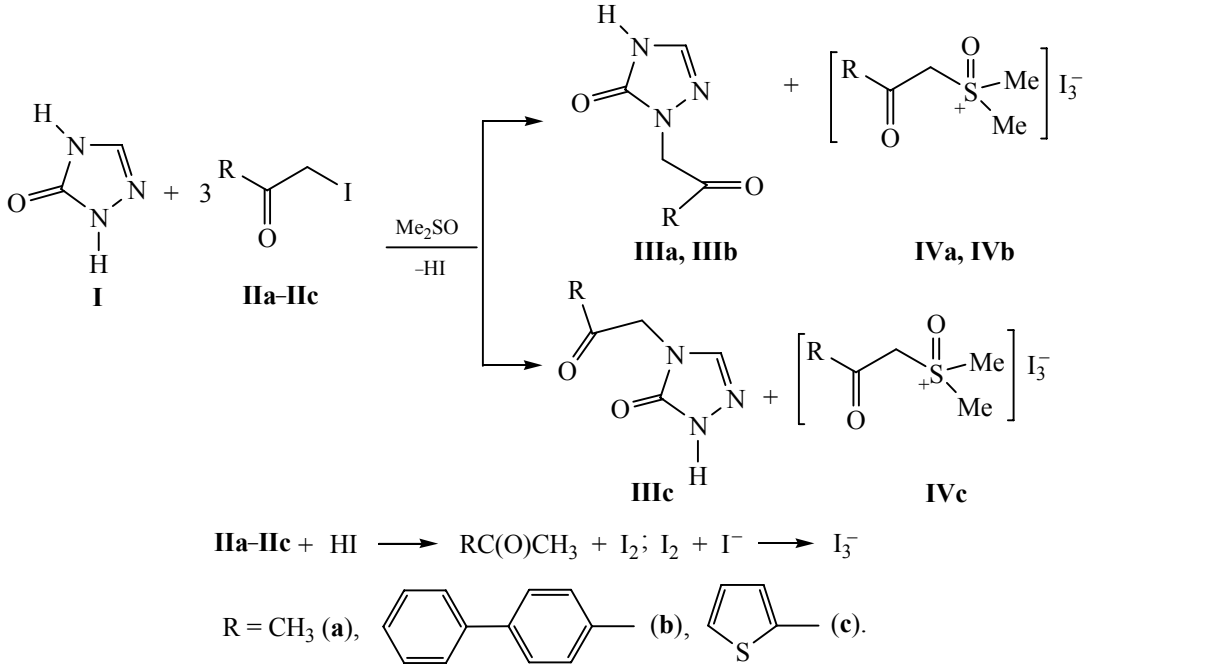
We have previously shown that α-iodoketones undergo readily alkylation with azoles, in which structure there is no carbonyl carbon atom, to form dialkylated products [14]. To evaluate the effect of a carbonyl group in the heterocycle structure on the direction and degree of the alkylation of triazolone with α-iodoketone, we have studied the reaction of 2,4-dihydro-3*H*-1,2,4-triazol-3-one **I** with 1-iodopropan-2-one **IIa**, 1-(1,1'-biphenyl)-4-yl-2-iodo-1-ethanone **IIb** and 2-iodo-1-(2-thienyl)-1-ethanone **IIc** at 20–25°C in the absence of catalyst in a DMSO medium. Choice of solvent was solely based on the solubility of the starting reagents.

Alkylation of compound **I** with 1-iodopropan-2-one **IIa** and 1-(1,1'-biphenyl)-4-yl-2-iodo-1-ethanone **IIb** occurs by the N^2 atom, and in the case of 2-iodo-1-(2-thienyl)-1-ethanone **IIc** – by the N^4 atom to form the previously unknown 2-(2-oxopropyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one **IIIa**, 2-[2-(1,1'-biphenyl)-4-yl-2-oxoethyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one **IIIb** and 4-[2-oxo-2-(2-thienyl)ethyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one **IIIc**, respectively.

Unreacted iodoketones **IIa**–**IIc** reacted with dimethyl sulfoxide, which resulted in the formation of previously unknown sulfoxonium triiodides **IVa**–**IVc**. Triiodide anion of the salts **IVa–IVc** was formed due to the presence of elemental iodine, obtained at initial reduction of iodoketones **IIa**–**IIc** by iodinehydrogen that was formed via N^2- (**IIa, IIb**) and N^4- (**IIc**) alkylation. The UV spectra of triiodides **IVa**–**IVc** contain the absorption bands in the ranges of 292–293 and 361–362 nm, which are characteristic of anion (I_3^-) [15].

To conclude, we have shown that the high lability of the C–I bond in the α-iodoketones promotes the reactions of mono-N^2/N^4-alkylation of 2,4-dihydro-3*H*-1,2,4-triazol-3-one in the absence of solid bases and phase transfer catalysts. The presence of the carbonyl group in the structural fragment –NH–C(O)–NH– of triazolone prevents formation of the dialkylated product.

General procedure for alkylation of 2,4-dihydro-3*H*-1,2,4-triazol-3-one. A mixture of 0.01 mol of triazolone **I** and 0.03 mol of iodoketone **IIa**–**IIc** in 5 mL of DMSO was stirred at 25°C for 10–12 h. The reaction mixture was added dropwise to 300 mL of diethyl ether with stirring to remove DMSO. The resulting thick substance was dissolved in 5 mL of



acetone, and the precipitate (**IIIa–IIIc**) was filtered off, washed with acetone and dried in vacuum. To the filtrate was added 50 mL of hexane. The precipitate (**IVa**) or oil (**IVb**, **IVc**) was re-precipitated twice (acetone–hexane) and dried in vacuum.

2-(2-Oxopropyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (IIIa) was prepared from 0.85 g of triazolone **I** and 5.52 g of 1-iodopropan-2-one **IIa**. Yield 0.87 g (62%), yellow crystals, mp 121–125°C. IR spectrum, ν, cm^{-1}: 1705 (C=O); 2919, 1410 (CH_2); 3270 (NH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 5.64 s (2H, CH_2), 7.74 s (1H, H^5), 11.33 (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 26.37 (CH_3), 54.77 (CH_2), 136.75 (C^5), 154.2 ($C{=}O_{het}$), 203.46 (C=O). ^{15}N NMR spectrum, δ_N, ppm: –114.2 (N^1), –197.1 (N^2), –237.4 (N^4). Found, %: C 43.03; H 5.07; N 29.16. $C_5H_7N_3O_2$. Calculated, %: C 42.55; H 5.00; N 29.78.

2-[2-(1,1'-Biphenyl)-4-yl-2-oxoethyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (IIIb) was prepared from 0.85 g of triazolone **I** and 9.66 g of 1-(1,1'-biphenyl)-4-yl-2-iodo-1-ethanone **IIb**. Yield 1.08 g (39%), pale yellow crystals, mp 95–102°C. IR spectrum, ν, cm^{-1} 1702 (C=O), 2844, 1405 (CH_2); 3138 (NH). ^1H NMR spectrum, δ, ppm: 5.49 s (2H, CH_2), 7.70 s (1H, H^5), 7.41–8.12 m (9H, biphenyl), 11.32 (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 52.74 (CH_2), 136.05 (C^5), 126.89–144.79 (biphenyl), 155.7 ($C{=}O_{het}$), 198.64 (C=O). ^{15}N NMR spectrum, δ_N, ppm: –111.8 (N^1), –193.3 (N^2), –241.4 (N^4). Found, %: C 68.19; H 5.03; N 14.74. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.80; H 4.69; N 15.05.

4-[2-Oxo-2-(2-thienyl)ethyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (IIIc) was prepared from 0.85 g of triazolone **I** and 7.56 g of 2-iodo-1-(2-thienyl)-1-ethanone **IIc**. Yield 0.97 g (46%), mp 179–182°C. IR spectrum, ν, cm^{-1}: 1708 (C=O), 2847, 1443 (CH_2), 3153 (NH). ^1H NMR spectrum, δ, ppm: 5.29 s (2H, CH_2), 7.66 s (1H, H^5), 7.30–8.11 m (3H, thienyl), 11.26 (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 52.12 (CH_2), 136.7 (C^5), 133.3, 136.6, 138.2, 140.2 (thienyl), 156.33 ($C{=}O_{het}$), 193.02 (C=O). ^{15}N NMR spectrum, δ_N, ppm: –115.7 (N^1), –212.2 (N^2), –263.8 (N^4). Found, %: C 45.98; H 3.82; N 20.15; S 15.85. $C_8H_7N_3O_2S$. Calculated, %: C 45.92; H 3.37; N 20.08; S 15.33.

2-Oxopropyldimethylsulfoxonium triiodide (IVa). Yield 3.92 g (76%) [from 1.84 g (0.01 mol) of **IIa**], brown powder, mp 70–71°C. IR spectrum, ν, cm^{-1}: 1709 (C=O), 2891, 1407 (CH_2). ^1H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 4.76 s (2H, CH_2), 3.47 s (6H, CH_3S). ^{13}C NMR spectrum, δ_C, ppm: 29.60 (CH_3), 31.55 (CH_3S), 78.99 (CH_2), 200.27 (C=O). UV spectrum (CH_3CN), λ_{max}, nm: 292, 361 (I_3^-). Found, %: C 12.20; H 2.13; I 74.25; S 6.08. $C_5H_{11}I_3O_2S$. Calculated, %: C 11.64; H 2.15; I 73.79; S 6.21.

2-Oxo-2-(2-biphenyl)ethyldimethylsulfoxonium triiodide (IVb). Yield 4.51 g (69%) [from 3.22 g

(0.01 mol) of **IIb**], dark brown oil. IR spectrum, ν, cm^{-1}: 1680 (C=O), 2918, 1417 (CH_2). ^1H NMR spectrum, δ, ppm: 4.85 s (2H, CH_2), 3.31 s (6H, CH_3S), 7.46–8.01 m (9H, biphenyl). ^{13}C NMR spectrum, δ_C, ppm: 39.50 (CH_3), 65.38 (CH_2), 126.9–146.2 (biphenyl), 190.6 (C=O). UV spectrum (CH_3CN), λ_{max}, nm: 293, 362 (I_3^-). Found, %: C 28.87; H 2.90; I 57.71; S 4.62. $C_{16}H_{17}I_3O_2S$. Calculated, %: C 29.38; H 2.63; I 58.21; S 4.90.

2-Oxo-2-(2-thienyl)ethyldimethylsulfoxonium triiodide (IVc). Yield 3.79 g (65%) [from 2.52 g (0.01 mol) of **IIc**], dark brown oil. IR spectrum, ν, cm^{-1}: 1714 (C=O), 2918, 1410 (CH_2). ^1H NMR spectrum, δ, ppm: 4.66 s (2H, CH_2), 3.38 s (6H, CH_3S), 7.19–7.92 m (3H, thienyl). ^{13}C NMR spectrum, δ_C, ppm: 39.55 (CH_3), 65.69 (CH_2), 129.25, 133.32, 135.04, 140.85 (thienyl), 183.9 (C=O). UV spectrum (CH_3CN), λ_{max}, nm: 292, 363 (I_3^-). Found, %: C 16.96; H 2.15; I_3 65.73; S 10.49. $C_8H_{11}I_3O_2S_2$. Calculated, %: C 16.45; H 1.90; I_3 65.19; S 10.98.

IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. ^1H, ^{13}C, ^{15}N NMR spectra were registered on a Bruker DPX-400 instrument [400.13 (^1H), 100.61 (^{13}C), 40.56 (^{15}N) MHz] relative to internal TMS using DMSO-d_6 as solvent. Elemental analysis was performed on an automated CHNS-analyzer Thermo scientific Flash 2000. Melting points were determined on a Micro-Hot-Stage PolyTherm A instrument. UV spectra were obtained on a UV-Vis Lambda 35 spectrophotometer.

The main results were obtained with use of material and technical base of the Baikal Analytical Center for Collective Use of the Siberian Branch of the Russian Academy of Sciences.

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