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1-HETARYLTRIAZENES IN THE SYNTHESIS OF CONDENSED MESOIONIC 1,2,3-TRIAZOLIO-5-OLATES

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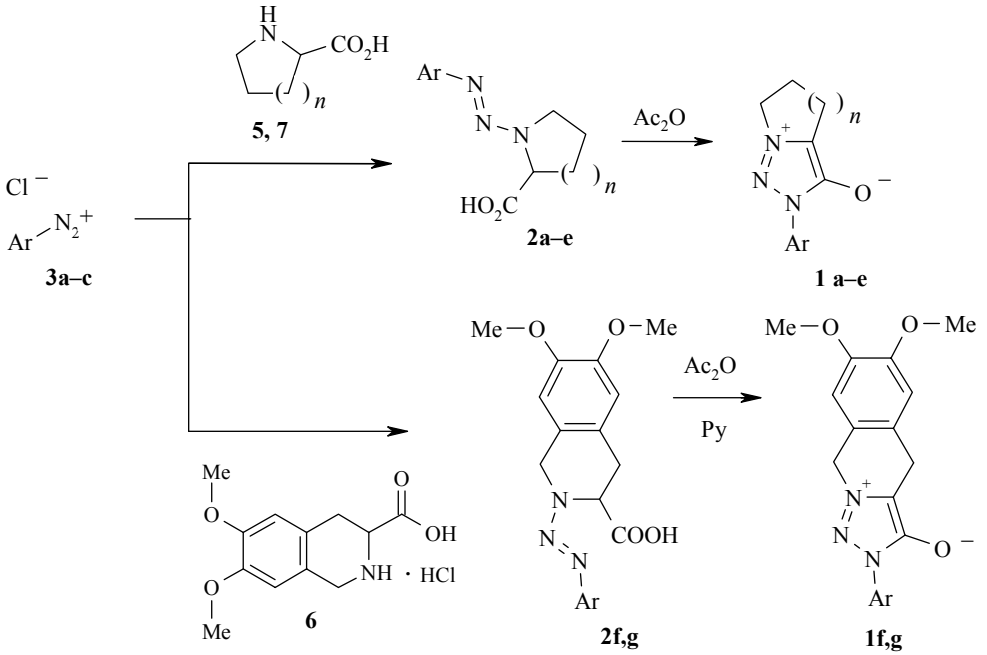
Condensed mesoionic 1,2,3-triazoles containing an aryl or hetaryl substituent at $N_{(2)}$ in the ring have been synthesized by intramolecular condensation.

Keywords: imidazole, mesoionic heterocycles, triazenes, 1,2,3-triazole, intramolecular condensation.

Several approaches are known for the synthesis of monocyclic mesoionic heterocycles [1, 2], while the number of reported mesoionic condensed heterocycles is very limited [3-5]. Mesoionic 1,2,3-triazoles condensed with a six-membered ring hold interest for to their biological properties [6-8]. One of the methods for the synthesis of 1,2,3-triazolio-5-olates [9] involves the intramolecular cyclization of triazenes [10], although only one example of a synthesis of a condensed mesoionic 1,2,3-triazole by this method has been reported [11].



1,2 a,c,f,g Ar = Ph, **b,d** Ar = C_6H_4F-4, **e** Ar = C_6H_4COOEt-4; **3 a** Ar = Ph, **b** Ar = C_6H_4F-4, **c** Ar = C_6H_4COOEt-4; **1,2 a,b** n = 1, **c–e** n = 2; **5** n = 1; **7** n = 2

* Dedicated to Academician M. G. Voronkov on his Eighty-Fifth Birthday.

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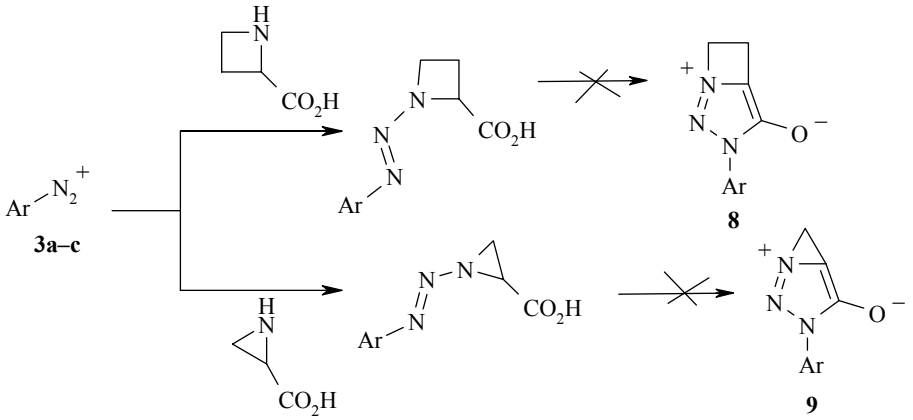
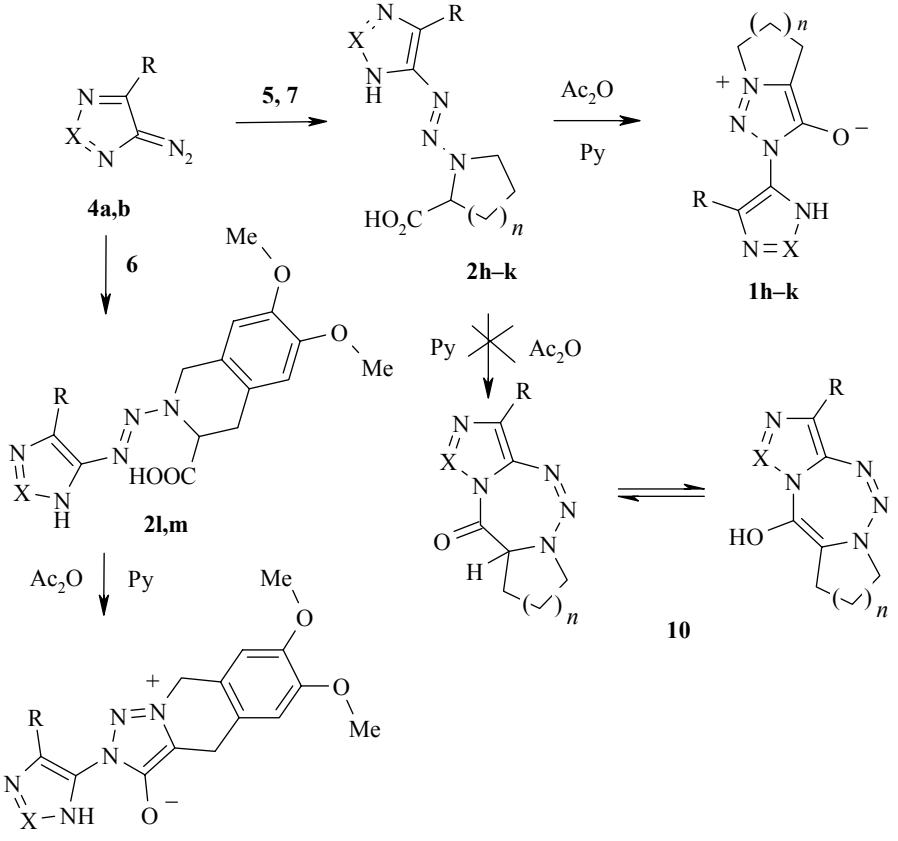
No such reactions have been reported for the synthesis of 1,2,3-triazoles containing heterocyclic substituents at $N_{(1)}$. In the present work, we report the synthesis of condensed mesoionic [1,2,3]triazoles **1** starting from triazenes **2** generated from diazonium salts of aromatic **3** or heterocyclic diazo compounds **4** and cyclic α-amino acids, namely, 2-aziridinecarboxylic acid, 2-azetidinecarboxylic acid, proline **5**, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **6**, and pipecolinic acid **7**.



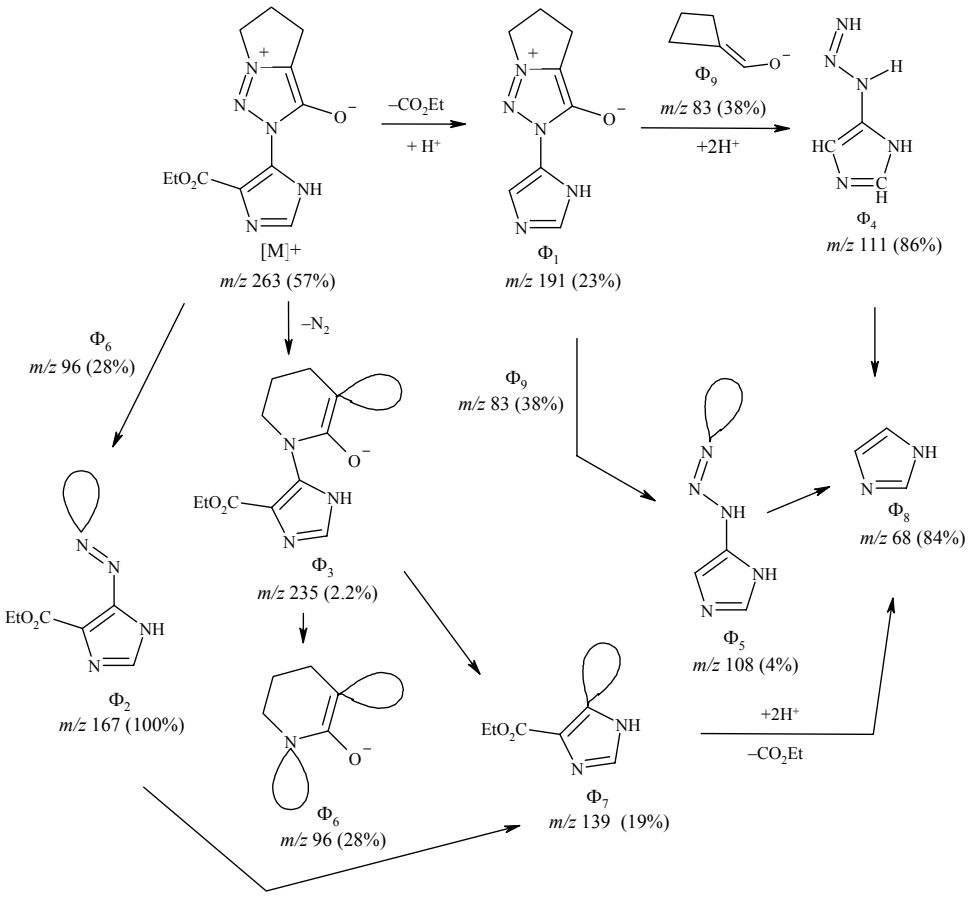
We have shown that mesoionic triazoles are formed only upon condensation to five- and six-membered heterocycles. Mesoionic heterocycles **8** and **9** are not formed upon treating triazenes obtained from 1-aziridinecarboxylic and 2-azetidinecarboxylic acids with acetic anhydride. This failure is presumably related to the instability of the resultant condensed rings **8** and **9** as a consequence of strain of the C–C bonds in the small rings.



1, 2 h,j,l R = CO_2Et, X = CH; **i,k,m** R = $CONHC_6H_{11}$-*cyclo*, X = N; **h,i** *n* = 1, **j–m** *n* = 2

Intramolecular condensation to give 1,2,3,4-tetrazepins **10** is possible in the case of triazenes **2h-m** containing 1H-1,2,3-triazole (**4a**) or 1H-imidazole (**4b**) at $N_{(3)}$. However, we have shown that these compounds yield the more stable mesoionic 1,2,3-triazoles **1h-m**. Thus, for example, the azo coupling reaction of 5-diazoimidazole **4b** with proline **5** gives triazine **2b**, isolated as two positional isomers relative to the N=N bond. Intramolecular condensation in acetic anhydride leads to pyrrolo[1,2-*c*][1,2,3]triazolio-5-olate **1h**.

The ^{1}H NMR spectra of **1h-m** lack a methine proton signal, which should have been observed in the spectrum of **10**, but the signal for the acid proton at 11-13 ppm can be assigned both to the NH group proton and OH proton of the enolic form of **10**. In this case, the signal for the carbonyl (or enolic) carbon should be seen as a doublet split by the imidazole proton with J = 3-5 Hz in the ^{13}C NMR spectrum of products **10** obtained from diazoimidazole **4b**. However, the signal for the carbon atom attached to $N_{(3)}$ in the ring is seen as a singlet at 156 ppm. The mass spectrum of **1h** shows a molecular ion peak $[M]^+$ 263* (I = 57%) corresponding to the chemical formula. Elimination of a nitrogen molecule is characteristic for heterocycles containing an N=N fragment and the corresponding fragment ion peak has high intensity [12]. The molecular ion M^+ in the spectrum of **1h**, having eliminated a nitrogen molecule, decomposes to give fragment Φ_3 235 (2.2%), which then may decompose to give fragments Φ_6 96 (28%) and Φ_7 139 (19%). Also, the resultant fragment ion Φ_1 191 (I = 23%) eliminates $–CH_2–CH_2–CH_2–CH–C–O^-$ to give fragment Φ_4 111 (86%) and Φ_5 105 (4%). The third pathway for decomposition of the molecular ion proceeds initially to give fragment species Φ_2 167 (100%) and then with the loss of molecular nitrogen. The subsequent decomposition of fragment ions Φ_4, Φ_5, and Φ_7 proceeds to give imidazole Φ_8 68 (84%).



*Here and subsequently, the *m/z* (I_{rel}, %) values are given for the mass spectra.

Thus, we have shown that a broad range of mesoionic 1,2,3-triazole derivatives may be obtained by the intramolecular condensation of triazenes.

EXPERIMENTAL

The reaction course and purity of the products were checked by thin-layer chromatography on Silufol UV-254 plates using 1:10 and 1:5 ethyl acetate–hexane as eluents. The NMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz for the ^{1}H NMR spectra and a Bruker DRX-400 spectrometer at 400 MHz for the ^{1}H NMR spectra and 100 MHz for the ^{13}C NMR spectra for solutions in DMSO-d_6 (the ^{13}C NMR spectrum of **1l**) and DMSO-d_6–CCl_4 for the other compounds. TMS served as the internal standard. The mass spectra were taken on a Varian MAT-311A mass spectrometer with 70 eV ionizing voltage and direct sample inlet into the ion source.

Preparation of zwitter-ionic triazoles 1 from triazenes 2 (general method). A solution of 0.186 g (2.7 mmol) sodium nitrite in a minimal volume of water was added dropwise to a stirred solution of 1.1 mmole aromatic amine in 0.54 ml (2.7 mmol) 5 N hydrochloric acid at 0-5°C. The reaction endpoint was monitored using iodine–starch paper. The yellow diazo compound solution obtained was added dropwise to a solution of 1.1 mmol N-substituted α-amino acid in 1 N aq. NaOH cooled to 0-5°C. The solution turned dark red. Concentrated hydrochloric acid was added to bring the solution to pH 4 and the precipitate formed was filtered off. The triazene obtained was dissolved in 5 ml pyridine and 5 ml acetic anhydride. The reaction mixture turned a dark black–brown and was left stand for 15 h at room temperature. The solvent was evaporated off in vacuum. The residue was dissolved in water and extracted with three 15-ml chloroform portions. The organic extract was evaporated in vacuum. Hexane was added to a minimal volume of chloroform to give a precipitate, which was filtered off and washed with hexane.

1-Phenyl-2,4,5,6-tetrahydropyrrolo[1,2-*c*][1,2,3]triazolio-5-olate (1a) was obtained in 69% yield (0.152 g), mp 107°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.98 (2H, d, *J* = 8.7, ArH), 7.43 (2H, dd, *J* = 7.5, ArH), 7.28 (1H, t, *J* = 7.5, ArH), 4.35 (2H, t, *J* = 7.4, CH_2), 2.87 (2H, t, *J* = 7.6, CH_2), 2.63 (2H, tt, *J* = 7.4, *J* = 7.6, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 201 (48). Found, %: N 20.53. $C_{11}H_{11}N_3O$. Calculated, %: N 20.89.

2-(4-Fluorophenyl-2,4,5,6-tetrahydropyrrolo[1,2-*c*][1,2,3]triazolio-5-olate (1b) was obtained in 68% yield (0.16 g), mp 57°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.00 (2H, dd, *J* = 12.1, *J* = 6.4, ArH), 7.20 (2H, dd, *J* = 9.3, *J* = 8.7, ArH), 4.36 (2H, t, *J* = 7.3, CH_2), 2.87 (2H, t, *J* = 6.4, CH_2), 2.64 (2H, tt, *J* = 7.3, *J* = 6.4, CH_2). ^{13}C NMR spectrum, δ, ppm: 161.43 (dt, ^1J_F = 243.8, *J* = 6.0, C-*p*), 153.81 (s, $C_{(3)}$), 134.27 (dt, ^4J_F = 2.7, *J* = 7.9, C-*i*), 123.20 (ddd, ^3J_F = 8.4, *J* = 173.6, *J* = 7.4, C-*o*), 122.67 (ttt, *J* = 5.5, *J* = 5.2, *J* = 3.4, $C_{(3a)}$), 116.87 (ddd, ^2J_F = 8.4, *J* = 170.5, *J* = 8.9, C-*m*), 50.91 (ttt, *J* = 148.6, *J* = 2.6, *J* = 2.7, $C_{(6)}$), 25.90 (ttt, *J* = 135.5, *J* = 3.1, *J* = 2.7, $C_{(4)}$), 22.73 (ttt, *J* = 136.1, *J* = 3.4, *J* = 2.3, $C_{(5)}$). Mass spectrum, *m/z* (I_{rel}, %): 219 (87). Found, %: N 18.60. $C_{11}H_{10}FN_3O$. Calculated, %: N 19.17.

2-Phenyl-4,5,6,7-tetrahydro-2H-[1,2,3]triazolo[1,5-*a*]pyridinio-3-olate (1c) was obtained in 47% yield (0.117 g), mp 118°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.00 (2H, dd, *J* = 8.7, *J* = 1.2, ArH), 7.51 (2H, dd, *J* = 8.1, *J* = 7.6, ArH), 7.36 (1H, t, *J* = 7.4, ArH), 4.25 (2H, t, *J* = 6.0, CH_2), 2.55 (2H, t, *J* = 6.3, CH_2), 2.03-1.96 (2H, m, CH_2), 1.86-1.81 (2H, m, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 215 (70). Found, %: N 19.33. $C_{12}H_{13}N_3O$. Calculated, %: N 19.52.

2-(4-Fluorophenyl)-4,5,6,7-tetrahydro-2H-[1,2,3]triazolo[1,5-*a*]pyridinio-3-olate (1d) was obtained in 71% yield (0.182 g), mp 135°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.10-8.00 (2H, m, ArH), 7.30-7.12 (2H, m, ArH), 4.22 (2H, t, *J* = 6.1, CH_2), 2.61 (2H, t, *J* = 6.1, CH_2), 2.15-1.99 (2H, m, CH_2), 1.98-1.83 (2H, m, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 233 (74). Found, %: N 18.32. $C_{12}H_{12}FN_3O$. Calculated, %: N 18.02.

1-(4-Ethoxycarbonylphenyl)-4,5,6,7-tetrahydro-2H-[1,2,3]triazolo[1,5-*a*]pyridinio-3-olate (1e) was obtained in 55% yield (0.174 g), mp 135°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.22 (2H, d, *J* = 8.8, ArH),

8.05 (2H, d, J = 8.9, ArH), 4.33 (2H, q, J = 7.2, OCH_2), 4.25 (2H, t, J = 6.4, CH_2), 2.62 (2H, J = 6.4, CH_2), 2.22-2.02 (2H, m, CH_2), 2.00-1.82 (2H, m, CH_2), 1.39 (3H, t, J = 7.2, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 287 (39). Found, %: N 14.26. $C_{15}H_{17}N_3O_3$. Calculated, %: N 14.62.

7,8-Dimethoxy-2-phenyl-5,10-dihydro-2H-[1,2,3]triazolo[1,5-*b*]isoquinolinio-3-olate (1f) was obtained in 62% yield (0.220 g), mp 107°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.03 (2H, d, J = 7.6, C_6H_5), 7.51 (1H, s, ArH), 7.50 (2H, dd, J = 7.7, J = 7.6, C_6H_5), 7.41 (1H, s, ArH), 7.38 (1H, t, J = 7.6, C_6H_5), 6.94 (2H, s, CH_2), 5.43 (2H, s, CH_2), 3.92 (3H, s, OCH_3), 3.81 (3H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %). Found, %: N 12.81. $C_{18}H_{17}N_3O_3$. Calculated, %: N, 13.00.

2-(4-Fluorophenyl)-7,8-dimethoxy-5,10-dihydro-2H-[1,2,3]triazolo[1,5-*b*]isoquinolinio-3-olate (1f) was obtained in 73% yield (0.274 g), mp 242°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.13-8.06 (2H, m, ArH), 7.30-7.21 (2H, m, ArH), 6.96 (1H, s, ArH), 6.94 (1H, s, ArH), 5.39 (2H, s, CH_2), 3.88 (2H, s, CH_2), 3.81 (3H, s, OCH_3), 3.80 (3H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 341 (95). Found, %: N 12.46. $C_{18}H_{16}FN_3O_3$. Calculated, %: N 12.32.

2-(4-Ethoxycarbonyl-1H-imidazol-5-yl)-2,4,5,6-tetrahydropyrrolo[1,2-*c*][1,2,3]triazolio-3-olate (1h) was obtained in 78% yield (0.225 g), mp 132°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 13.5 (1H, br. s, NH), 7.95 (1H, s, CH), 4.37 (2H, t, J = 7.5, CH_2), 4.15 (2H, q, J = 7.1, OCH_2), 2.78 (2H, t, J = 7.2, CH_2), 2.59 (2H, tt, J = 7.5, J = 7.2, CH_2), 1.15 (3H, t, J = 7.1, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 263 (57). Found, %: N 26.80. $C_{11}H_{13}N_5O_3$. Calculated, %: N 26.60.

2-(4-Cyclohexylaminocarbonyl-1H-1,2,3-triazol-5-yl)-2,4,5,6-tetrahydropyrrolo[1,2-*c*][1,2,3]-triazolio-3-olate (1i) was obtained in 27% yield (0.094 g), mp, 71°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.54 (1H, d, J = 5.6, CONH), 7.39 (1H, br. s, NH), 4.96 (2H, t, J = 6.2, CH_2), 2.98-2.88 (1H, m, CH), 2.85-2.74 (2H, m, CH_2), 2.00-1.92 (8H, m, CH_2), 1.61-1.22 (4H, m, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 317 (60). Found, %: N 30.73. $C_{14}H_{19}N_7O_2$. Calculated, %: N 30.90.

2-(4-Ethoxycarbonylimidazol-1-yl)-4,5,6-tetrahydro-2H-[1,2,3]triazolo[1,5-*a*]pyridinio-3-olate (1j) was obtained in 62% yield (0.189 g). ^{1}H NMR spectrum, δ, ppm (J, Hz): 13.6 (1H, br. s, NH), 7.76 (1H, s, CH), 4.59 (2H, t, J = 6.2, CH_2), 4.22 (2H, t, J = 7.2, OCH_2), 2.79 (2H, t, J = 7.2, CH_2), 2.15-1.86 (4H, m, CH_2), 1.18 (3H, t, J = 7.2, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 172.05 (q, J = 6.6, CO_2), 159.19 (br. s, $C_{im\text{-}4}$), 156.07 (t, J = 1.5, $C_{(3)}$), 149.19 (br. s, $C_{(7)}$), 148.62 (br. s, $C_{(6)}$), 138.13 (d, J = 213.0, $CH_{im\text{-}2}$), 122.83 (br. s, $C_{(8)}$), 110.66 (br. s, s, $C_{im\text{-}5}$), 118.91 (br. s, $C_{(4a)}$), 113.00 (d, J = 162.0, $C_{(5)}$), 112.53 (d, J = 170.8, $C_{(8)}$, 110.66 (br. s, $C_{(3a)}$), 61.04 (tq, J = 148.5, J = 4.3, OCH_2), 56.60 (q, J = 144.4, OCH_3), 56.61 (q, J = 144.4, OCH_3), 50.72 (td, J = 143.5, J = 5.5, $C_{(9)}$, 25.00 (td, J = 133.2, J = 0.8, $C_{(4)}$), 14.64 (qt, J = 127.1, J = 2.7, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 277 (60). Found, %: N 25.13. $C_{12}H_{15}N_5O_3$. Calculated, %: N 25.27.

2-(4-Cyclohexylaminocarbonyl-1H-1,2,3-triazol-5-yl)-4,5,6,7-tetrahydro-2H-[1,2,3]triazolo[1,5-*a*]-pyridinio-3-olate (1k) was obtained in 27% yield (0.098 g), mp 82°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.54 (1H, d, J = 5.6, CONH), 7.38 (1H, br. s, NH), 4.96 (2H, t, J = 6.2, CH_2), 2.98-2.70 (3H, m, CH+CH_2), 2.10-1.74 (10H, m, CH_2), 1.61-1.22 (4H, m, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 331 (55). Found, %: N 29.22. $C_{15}H_{21}N_7O_2$. Calculated, %: N 29.59.

2-(4-Ethoxycarbonyl-1H-imidazol-5-yl)-7,8-dimethoxy-5,10-dihydro-2H-[1,2,3]triazolo[1,5-*b*]-isoquinolinio-3-olate (1l) was obtained in 59% yield (0.250 g), mp 163°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 12.2 (1H, br. s, NH), 7.74 (1H, s, CH_{im}), 6.95 (1H, s, ArH), 6.94 (1H, s, ArH), 5.38 (2H, s, CH_2N), 4.15 (2H, q, J = OCH_2), 1.12 (3H, t, J = 7.2, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 159.19 (br. s, $C_{(3)}$), 156.07 (t, J = 1.5, CO_2), 149.19 (br. s, $C_{(7)}$), 148.62 (br. s, $C_{(6)}$), 138.13 (d, J = 213.0, $CH_{im\text{-}2}$), 122.83 (br. s, $C_{(8a)}$), 121.27 (br. s, $C_{im\text{-}4}$), 118.91 (br. s, $C_{(4a)}$), 113.00 (d, J = 162.0, $C_{(5)}$), 112.53 (d, J = 170.8, $C_{(8)}$), 111.42 (br. s, $C_{im\text{-}5}$), 110.66 (br. s, $C_{(3a)}$), 61.04 (tq, J = 148.5, J = 4.3, OCH_2), 56.60 (q, J = 144.4, OCH_3), 56.61 (q, J = 144.4, OCH_3), 50.72 (td, J = 143.5, J = 5.5, $C_{(9)}$), 25.00 (td, J = 133.2, J = 0.8, $C_{(4)}$), 14.64 (qt, J = 127.1, J = 2.7, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 384 [M - 1] (25). Found, %: N 18.06. $C_{18}H_{19}N_5O_5$. Calculated, %: N 18.17.

2-(4-Cyclohexylaminocarbonyl-1H-1,2,3-triazol-7,8-dimethoxy-5-yl)-5,10-dihydro-2H-[1,2,3]-triazolo[1,5-*b*]isoquinolinio-3-olate (1m) was obtained in 73% yield (0.352 g), mp 137°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.21 (1H, br. s, NH), 8.90 (1H, d, *J* = 5.6, CONH), 7.31 (1H, s, ArH), 6.99 (1H, s, ArH), 5.40 (2H, s, CH_2), 4.30 (2H, s, CH_2), 3.94 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.90-3.02 (1H, m, CH), 2.05-1.54 (8H, m, CH_2), 1.50-1.04 (2H, m, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 439 (28). Found, %: N 22.11. $C_{21}H_{25}N_7O_4$. Calculated, %: N 22.31.

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