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SYNTHESIS AND N-ALKYLATION OF DIETHYL 4,7-DIHYDROAZOLO[1,5-a]PYRIMIDIN-5,6-DICARBOXYLATES

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Key words: ternary condensation; diethyl 4,7-dihydroazolo[1,5-a]pyrimidin-5,6-dicarboxylates; Biginelli reaction; alkylation; C-functionalization; benzyl position

It has been shown that the ternary condensation of oxaloacetic ester (diethyl 2-oxosuccinate), aromatic aldehydes and 3-amino-1,2,4-triazole or 5-aminotetrazole in dimethylformamide results in formation of the corresponding diethyl 7-aryl-4,7-dihydroazolo[1,5-a]pyrimidin-5,6-dicarboxylates. By ^{1}H NMR spectroscopy (according to the data of the chemical shifts of C(2)H-protons for the corresponding N(4)H- and N(4)-methylderivatives of 7-phenyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-5,6-dicarboxylate) it has been found that alkylation of 4,7-dihydro[1,2,4]azolo[1,5-a]pyrimidin-5,6-dicarboxylates in the acetonitrile–saturated water alkali system leads selectively to formation of N(4)-alkyl derivatives. Both the starting compounds obtained and their N(4)-methylsubstituted analogues together with relative diethyl 4-aryl-3,4-dihydropyrimidin-2(1H)-on-5,6-dicarboxylates, 6-unsubstituted 4-aryl-3,4-dihydropyrimidin-2(1H)-on-5-dicarboxylates and the derivatives of 6-COR-7-aryl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidines are the promising objects for studying benzyl C(7)-functionalization of 4,7-dihydroazolo[1,5-a]pyrimidines, as well as of reactions associated with the presence of double C=C-bonds activated by two electron withdrawing groups. Obtaining of the key N(4)H- and N(4)Me-derivatives of 7-phenyl-4,7-dihydro[1,2,4]triazolo- and tetrazolo[1,5-a]pyrimidin-5,6-dicarboxylates also opens the way to the research of biological properties of the compounds of this class. It is noteworthy that being a three-component one the reaction studied, without any doubts, are appropriate for the synthesis of the derivatives of 7-aryl-4,7-dihydro[1,2,4]triazolo- and tetrazolo[1,5-a]pyrimidines containing two electron withdrawing substituents in positions 5 and 6.

СИНТЕЗ ТА N-АЛКІЛУВАННЯ ДІЕТИЛ 4,7-ДИГІДРОАЗОЛО[1,5-a]ПІРИМІДИН-5,6-ДИКАРБОКСИЛАТІВ
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Ключові слова: *трикомпонентна конденсація; діетил 4,7-дигідроазоло[1,5-a]піримідин-5,6-дикарбоксилати; реакція Біджинеллі; алкілування; С-функціоналізація; бензильне положення*
Показано, що трикомпонентна конденсація щавлевооцтового естеру (діетил 2-оксосукцинату), ароматичних альдегідів та 3-аміно-1,2,4-триазолу або 5-амінотетразолу в диметилформаміді призводить до утворення відповідних діетил 4,7-дигідроазоло[1,5-a]піримідин-5,6-дикарбоксилатів. За допомогою ^{1}H ЯМР-спектроскопії (за даними про хімічні зсуви сигналів протонів С(2)Н для відповідних N(4)H- та N(4)Me-похідних діетил 7-феніл-4,7-дигідро[1,2,4]триазоло[1,5-a]піримідин-5,6-дикарбоксилатів) встановлено, що алкілування 4,7-дигідроазоло[1,5-a]піримідин-5,6-дикарбоксилатів у системі ацетонітрил-насичений водний луг селективно призводить до утворення N(4)-алкілпохідних. Як отримані вихідні сполуки, так і їхні N(4)-метилзаміщені аналоги поряд зі спорідненими діетил 4-арил-3,4-дигідропіримідин-2(1H)-он-5,6-дикарбоксилатами, 6-незаміщеними етил 4-арил-3,4-дигідропіримідин-2(1H)-он-5-карбоксилатами та похідними 6-COR-7-арил-4,7-дигідро[1,2,4]триазоло[1,5-a]піримідинів є перспективними об'єктами для вивчення бензильної С(7)-функціоналізації 4,7-дигідроазоло[1,5-a]піримідинів, а також реакцій, пов'язаних з наявністю подвійного С=С-зв'язку, активованого двома акцепторними групами. Отримання ключових N(4)H- і N(4)Me-похідних 7-феніл-4,7-дигідро[1,2,4]триазоло- та тетразоло[1,5-a]піримідин-5,6-дикарбоксилатів також відкриває шлях до біологічних досліджень сполук цього класу. Відзначимо, що досліджена реакція, будучи трикомпонентною, безумовно підходить для синтезу та дослідження комбінаторних бібліотек похідних 7-арил-4,7-дигідро[1,2,4]триазоло- та тетразоло[1,5-a]піримідинів, що містять два електроноакцепторні замісники у положеннях 5 та 6.

СИНТЕЗ И N-АЛКИЛИРОВАНИЕ ДИЭТИЛ 4,7-ДИГИДРОАЗОЛО[1,5-a]ПИРИМИДИН-5,6-ДИКАРБОКСИЛАТОВ
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Ключевые слова: *трехкомпонентная конденсация; диэтил 4,7-дигидроазоло[1,5-a]пиримидин-5,6-дикарбоксилаты; реакция Биджинелли; алкилирование; С-функционализация; бензильное положение*
Показано, что трехкомпонентная конденсация щавелевоуксусного эфира (диэтил 2-оксосукцината), ароматических альдегидов и 3-амино-1,2,4-триазола или 5-аминотетразола в диметилформамиде приводит к образованию соответствующих диэтил 7-арил-4,7-дигидроазоло[1,5-a]пиримидин-5,6-дикарбоксилатов. С помощью ^{1}H ЯМР-спектроскопии (по данным химических сдвигов сигналов протонов С(2)Н для соответствующих N(4)H- и N(4)Me-производных диэтил 7-фенил-4,7-дигидро[1,2,4]триазоло[1,5-a]пиримидин-5,6-дикарбоксилата) установлено, что алкилирование 7-арил-4,7-дигидроазоло[1,5-a]пиримидин-5,6-дикарбоксилатов в системе ацетонитрил-насыщенная водная щелочь селективно приводит к образованию N(4)-алкилпроизводных. Как полученные исходные соединения, так и их N(4)-метилзамещенные аналоги наряду с родственными диэтил 4-арил-3,4-дигидропиримидин-2(1H)-он-5,6-дикарбоксилатами, 6-незамещенными этил 4-арил-3,4-дигидропиримидин-2(1H)-он-5-карбоксилатами и производными 6-COR-7-арил-4,7-дигидро[1,2,4]триазоло[1,5-a]пиримидинов являются перспективными объектами для изучения бензильной С(7)-функционализации 4,7-дигидроазоло[1,5-a]пиримидинов,

а также реакций, связанных с наличием двойной C=C-связи, активированной двумя акцепторными группами. Получение ключевых N(4)H- и N(4)Me-производных 7-фенил-4,7-дигидро[1,2,4]триазоло- и тетразоло[1,5-a]пиримидин-5,6-дикарбоксилатов также открывает путь к биологическим исследованиям соединений этого класса. Заметим, что исследованная реакция, являясь трехкомпонентной, безусловно подходит для синтеза и исследования комбинаторных библиотек производных 7-арил-4,7-дигидро[1,2,4]триазоло- и тетразоло[1,5-a]пиримидинов, содержащих два электроноакцепторных заместителя в положениях 5 и 6.

Previously we reported about the synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives of type **1** and **2** (Fig. 1). These substances (especially N-alkylated compounds **1b**, **2f,g**) are the promising objects for C(4)-functionalization of the 3,4-dihydropyrimidin-2(1H)-one cycle and contain the activated C=C-bond. Searching for the similar structures, which are more suitable for introduction of substituents in the benzyl position than compounds **1** and **2**, we drew attention to the derivatives of 4,7-dihydroazolo[1,5-a] pyrimidines of type **3** [3-7]. The absolute advantage of these compounds is high stability of the triazole cycle toward the action of nucleophilic reagents. At the same time, the obvious drawbacks of the objects of type **3** are: a) the presence of the alternative allyl position in the structure (6-methyl group); b) non-selectivity of alkylation of the compounds of type **3a** [8]; c) the possible insufficient activation of the benzyl position; d) the presence of C(2)-atom in the triazole cycle, which is able to be metallated under the action of *n*-BuLi or LDA.

However, the compounds of type **4b** should not have these disadvantages: a) the allyl (benzyl) position is the only one in the structure; b) alkylation of such compounds should be selective due to additional activation with 6-ethoxycarbonyl group; c) the benzyl position is also activated by withdrawing a substituent in position 6; d) there is no hydrogen atom being able to be metallated in the heterocycle (for tetrazole derivatives).

Thus, the aim of the study was the synthesis of the compounds of type **4a** (Ar = Ph) and the study of their methylation.

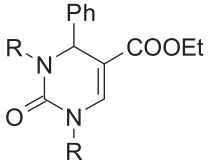
Diethyl 4,7-dihydroazolo[1,5-a]pyrimidin-5,6-dicarboxylates **5a,b** were synthesized by ternary condensation of aminoazoles, benzaldehyde and oxaloacetic ester (OAE) in HOAc (Scheme 1). This approach has worked well for the synthesis of 5-COR-4-aryl-3,4-dihydropyrimidin-2(1H)-ones derivatives [9, 10] and along with Atwal modification of Biginelli reaction is widely used in laboratory practice [11-14].

^{1}H NMR-spectra of the compounds obtained contain the signals of N(4)-protons in low fields, the signals of aromatic protons, the singlet of C(7)H-proton and the signals of two EtO-groups. Besides, for compound **5a** the signal of C(2)-proton at 7.70 ppm (separately from aromatic protons signals) is observed. It is also worth noting that the signal of one of the CH_2-groups (3.82-4.07 ppm for compound **5a**) like the spectrum of 6-acetyl-4-ethyl-5-methyl-7-phenyl-4,5-dihydro[1,2,4]triazolopyrimidine [8] is a multiplet, and it indicates its diastereotopism. Diastereotopism of the second CH_2-group does not reveal obviously because of the presence of flexible bonds between the ethoxycarbonyl group and the dihydrocycle, which contains a chiral centre, as well as due to a rather long distance from the CH_2-group to the chiral centre.

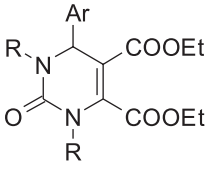
Alkylation of the compounds **5** obtained was studied in DMF/NaH and MeCN/KOH-H_2O systems. The second variant seemed to be the most convenient, and it allowed to isolate N-alkylderivatives with a good yield (Scheme 2).

It is interesting that unlike the above-mentioned alkylation of 6-acetyl-5-methyl-7-phenyl-4,5-dihydro[1,2,4]triazolopyrimidine [8] the process in this case occurred selectively (which was favoured by ^{1}H NMR-spectra of the products obtained). In contrast to the ^{1}H NMR spectrum of the initial compounds **5**, the signal of NH-protons is absent in a low field, but the signal of NCH_3-group is present.

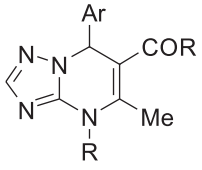
In our opinion, the only products of the reaction are exactly N(4)-methylderivatives (but not the possible N(3)-isomers). As evidence we give the following suggestion. For instance, the chemical shift of the signal of C(2) proton for compound **3c** is 7.63 ppm, for N(3)-methylderivative **3e** – 8.31 ppm (Fig. 2) [8]. The fact of such a considerable shift of the signal of



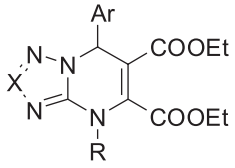
1 R = H (a); Me (b)



2 R = H (a-e), Me (f), Et (g); Ar = Ph (a,f,g), 4-BrC_6H_4 (b), 4-$MeOC_6H_4$ (c), 4-$NO_2C_6H_4$ (d), 4-$NMe_2C_6H_4$ (e)

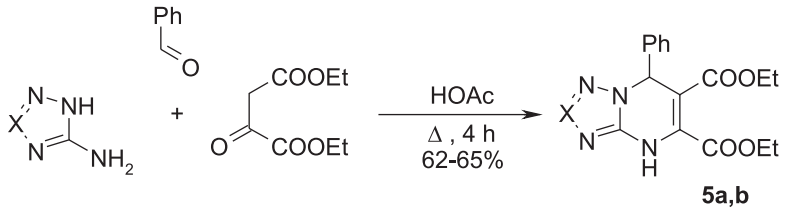


3 R = H (a), Me (b)

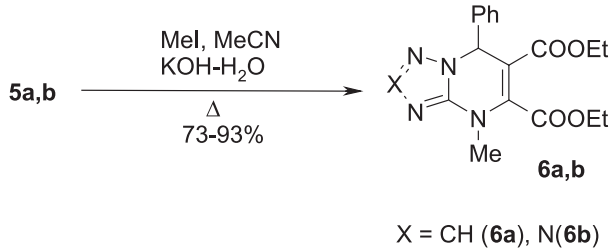


X = CH, N
4 R = H (a), Me (b)

Fig. 1. The known compounds and the objects of research.



Scheme 1. The synthesis of the starting compounds.



Scheme 2. Alkylation of compounds **5**.

the given proton, in our opinion, may be explained by the presence of the resonance form of type **3.1e**. Such a mesomer can not be for structure **3d**, so the chemical shifts for C(2) protons for compounds **3c** and **3d** do not differ fundamentally.

As it is seen in Fig. 2, the difference in the chemical shifts of C(2) protons for compounds **5a** and **6a** is only 0.07 ppm. This gives reason to believe that the alkylated product has exactly the structure of compound **6a**.

At the same time, IR-spectra of compounds **5** and **6** differ considerably: the broad bands corresponding to stretching vibrations of NH-bonds in the region of 2800-3300 Cm^{-1} are characteristic for compounds **5**. However, the similar signals are absent in IR-spectra of N-methylsubstituted **6a,b**. Furthermore, the change in the melting points of the compounds obtained is the evidence of disappearance (or decrease) of intermolecular H-bonds: 202-4°C (**5a**) → 103-5°C (**6a**) and 174-6ºC(**5b**) → 113-5°C (**6b**).

As the addition to the compounds previously obtained [1] we synthesized 6-unsubstituted 3,4-dihydropyrimidin-2(1H)-ones **1c,d** by the reaction of aromatic aldehydes, urea and ethyl 3,3-diethoxypropanoate in HOAc (Scheme 3).

It is noteworthy that the benzyl proton in the product **1d** obtained is additionally activated by the nitrogroup.

In conclusion, in this report we have completed the synthesis of ethyl 3,4-dihydropyrimidin-2(1H)-on-5-carboxylates, diethyl 3,4-dihydropyrimidin-2(1H)-on-5,6-dicarboxylates, diethyl 4,7-dihydro[1,2,4]triazolo- and tetrazolo[1,5-a]pyrimidin-5,6-dicarboxylates containing the activated benzyl position. It has been shown that alkylation of diethyl 4,7-dihydro [1,2,4]triazolo- and tetrazolo[1,5-a]pyrimidin-5,6-dicarboxylates occurs at position 4. These compounds, first of all, are useful objects for studying their ben-

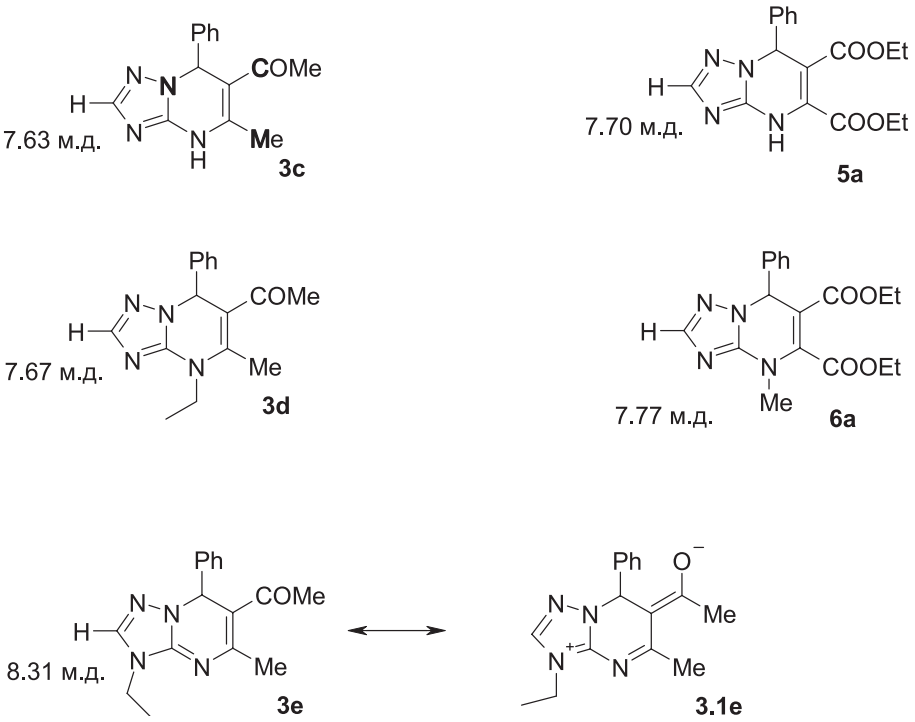
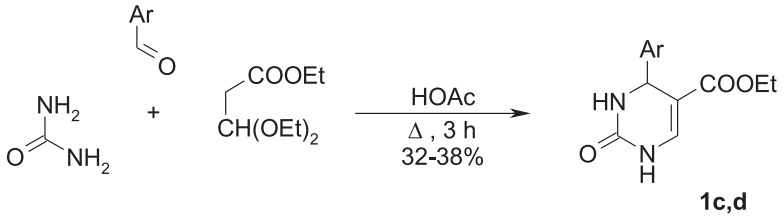


Fig. 2. Chemical shifts for the signals of C(2)-protons for the different types of structures.



Ar = 4-$MeOC_6H_4$(**1c**), 4-$O_2NC_6H_4$ (**1d**)

Scheme 3. The synthesis of 3,4-dihydropyrimidin-2(1H)-ones **1c,d**.

zyl functionalization, CH-acidity and the reactions with the activated C=C-bond. Therefore, the synthesis of the key structures mentioned opens the way to the research of biological activity of the compounds, as well as the study of their chemical properties. Moreover, being a three-component one the reaction studied, without any doubts, are useful for the combinatorial synthesis of various 4,7-dihydro[1,2,4]triazolo- and tetrazolo[1,5-a]pyrimidines' derivatives containing two electron withdrawing substituents in positions 5 and 6 of the heterocycle.

Experimental Part

^{1}H NMR spectra were recorded at 200 MHz using a Varian Mercury VX-200 spectrometer with $Si(CH_3)_4$ as an internal standard, chemical shifts are given in ppm, coupling constants are given in Hz. IR spectra were recorded in KBr pellets using a Specord IR-75 spectrometer. Elemental analyses were carried out using an EuroEA-3000 element analyzer. The purity of the compounds was checked by TLC (Merck ALUGRAM Xtra SIL G/UV 254 plates) with EtOAc-hexane and EtOAc-CH_2Cl_2 mixtures as eluents developing by UV-light and iodine vapours. Melting points were determined using a Köfler hot-stage apparatus. OAE was obtained, as pointed in the source [15], ethyl 3,3-diethoxyproponoate was synthesized by the method [8]. DMF was distilled under reduced pressure and stored under molecular sieves, HOAc was freezed for water deleting [16].

All the other reagents and solvents were commercially available and were purchased from SPE "Ukrorgsynthez".

Ethyl 4-aryl-3,4-dihydropyrimidin-2(1H)-on-5-carboxylates 1c,d. Boil the solution of ethyl 3,3-diethoxypropanoate (5.02 g, 26.4 mmol), urea (1.44 g, 24 mmol) and the corresponding aromatic aldehyde (24 mmol) in 20 ml of HOAc to reflux for 8 h. Remove the solvent under reduced pressure, boil the residue with 8-10 ml of EtOH for 10 min. Allow the mixture to crystallize for 12-18 h. Filter the precipitate and wash with EtOH.

Ethyl 4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-on-5-carboxylate (1c). Yield – 38%. M.p. – 159-161°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.16 (1H, d, *J* = 6.4, N(1)H), 7.63 (1H, br. s, N(3)H), 7.24 (1H, d, *J* = 6, C(6)H), 7.15 (2H, d, *J* = 8.8, ArH), 6.87 (2H, d, *J* = 8.8, ArH), 5.05 (1H, d, *J* = 2.8, C(4)H), 3.87-4.06 (2H, m, CH_2CH_3), 3.70 (3H, m, OCH_3), 1.1 (3H, t, *J* = 7.2, CH_2CH_3); IR spectrum (KBr), ν, cm^{-1}: 1616, 1652, 1698, 2915 (br), 3100, 3210, 3308. Found, %: C 61.05; H 6.01; N 9.98. $C_{14}H_{16}N_2O_4$. Calculated, %: C 60.86; H 5.84; N 10.14.

Ethyl 4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-on-5-carboxylate (1d). Yield – 32%. M.p. – 155-7°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.34 (1H, d, *J* = 6, N(1)H), 8.2 (2H, d, *J* = 8.6, ArH), 7.82 (1H, br. s, N(3)H), 7.51 (2H, d, *J* = 8.6, ArH), 7.29 (1H, d, *J* = 6, C(6)H), 5.25 (1H, d, *J* = 2.8, C(4)H), 3.84-4.09 (2H, m, CH_2CH_3), 1.09 (3H, t, *J* = 7.0, CH_2CH_3); IR spectrum (KBr), ν, cm^{-1}: 1349, 1521, 1651, 1683, 2928, 3108, 3300 (br). Found, %: C 53.80; H 4.67; N 14.22. $C_{13}H_{13}N_3O_5$. Calculated, %: C 53.61; H 4.50; N 14.43.

Diethyl 7-phenyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-5,6-dicarboxylate (5a). Boil the solution of 3-amino-1,2,4-triazole (1.47 g, 0.0175 mol), benzaldehyde (1.86 g, 0.0175 mol) and OAE (3 g, 0.0159 mol) in 14 ml of HOAc to reflux for 4 h. Cool the mixture, evaporate the solvent to dryness. Crystallize the oil obtained from EtOH (10 ml). Filter the precipitate, wash by 3 portions with 10 ml of EtOH each. Yield – 3.41 g (62%). M.p. – 202-4°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.67 (1H, br. s, N(4)H), 7.69 (1H, s, C(2)H), 7.01-7.50 (5H, m, Ph), 6.32 (1H, s, C(7)H), 4.26 (2H, q, *J* = 7.0, CH_2CH_3), 3.82-4.07 (2H, m, CH_2CH_3), 1.26 (3H, t, *J* = 7.0, CH_2CH_3), 0.99 (3H, t, *J* = 7.0, CH_2CH_3); IR spectrum (KBr), ν, cm^{-1}: 1557, 1595, 1712, 1739, 2784 (br), 2903, 2989, 3200, 3459 (br). Found, %: C 59.71; H 5.48; N 16.31. $C_{17}H_{18}N_4O_4$. Calculated, %: C 59.64; H 5.30; N 16.37.

Diethyl 7-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidin-5,6-dicarboxylate (5b). Boil the solution of 5-amino-1H-tetrazole (2.98 g, 0.035 mol), benzaldehyde (3.7 g, 0.035 mol) and OAE (6 g, 0.032 mol) in 30 ml of HOAc to reflux for 4 h. Cool the mixture and pour it into 200 ml of water, extract by 3 portions with 50 ml of EtOAc each. Wash the extract twice with 30 ml of water, dry over Na_2SO_4 and filter. Evaporate the filtrate under reduced pressure. Crystallize the oil obtained from EtOH (20 ml). Filter the precipitate, wash by three portions with 5 ml of EtOH-H_2O mixture (3:1) each. Yield – 7.23 g (65%). M.p. – 174-6°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.18 (1H, br. s, N(4)H), 7.22-7.49 (5H, m, Ph), 6.73 (1H, s, C(7)H),

4.30 (2H, q, J = 7.0, CH_2CH_3), 3.85-4.07 (2H, m, CH_2CH_3), 1.29 (3H, t, J = 7.0, CH_2CH_3), 0.99 (3H, t, J = 7.0, CH_2CH_3); IR spectrum (KBr), ν, cm^{-1}: 1593, 1713, 1738, 2906, 2993, 3053 (br), 3187, 3445. Found, %: C 56.11; H 5.09; N 20.21. $C_{16}H_{17}N_5O_4$. Calculated, %: C 55.97; H 4.99; N 20.40.

Diethyl 4-methyl-7-phenyl-4,7-dihydroazolo [1,5-a]pyrimidin-5,6-dicarboxylates (6a,b). Boil the mixture of the corresponding N(4)H-derivative **5a** or **5b** (8.74 mmol), MeI (3.3 ml, 52 mmol) and saturated water KOH solution (3 ml) in 30 ml of MeCN to reflux for 1 h. In the course of the reaction the precipitate of the starting compound was dissolved and KI precipitate was formed. Cool the mixture and pour it into 200 ml of 15% water solution of NaCl, extract by three portions with 40 ml of EtOAc each. Dry the extract with Na_2SO_4 and filter. After the solvent removal under the reduced pressure obtain the oil, recrystallize it from the minimal amount of EtOAc. Colourless precipitates of the reaction products were obtained.

Diethyl 4-methyl-7-phenyl-4,7-dihydro[1,2,4] triazolo[1,5-a]pyrimidin-5,6-dicarboxylate (6a). Yield – 73%. M.p. – 103-5°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.77 (1H, s, C(2)H), 7.15-7.44 (5H, m, Ph), 6.36 (1H, s, C(7)H), 4.37 (2H, q, J = 7.0, CH_2CH_3), 3.85-4.07 (2H, m, CH_2CH_3), 3.38 (3H, s, CH_3) 1.31 (3H, t, J = 7.0, CH_2CH_3), 1.01 (3H, t, J = 7.0, CH_2CH_3); IR spectrum (KBr), ν, cm^{-1}: 1562, 1632, 1699, 1744, 2909, 2989, 3252, 3379, 3475. Found, %: C 60.69; H 5.85; N 15.50. $C_{18}H_{20}N_4O_4$. Calculated, %: C 60.66; H 5.66; N 15.72.

Diethyl 4-methyl-7-phenyl-4,7-dihydrotetrazolo [1,5-a]pyrimidin-5,6-dicarboxylate (6b). Yield – 93%. M.p. – 113-5°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.28-7.43 (5H, m, Ph), 6.73 (1H, s, C(7)H), 4.39 (2H, q, J = 7.0, CH_2CH_3), 3.88-4.06 (2H, m, CH_2CH_3), 3.43 (3H, s, CH_3) 1.32 (3H, t, J = 7.0, CH_2CH_3), 0.99 (3H, t, J = 7.0, CH_2CH_3); IR spectrum (KBr), ν, cm^{-1}: 1558, 1635, 1710, 1745, 2939, 2985, 3397, 3462. Found, %: C 57.32, H 5.59; N 19.30. $C_{17}H_{19}N_5O_4$. Calculated, %: C 57.14; H 5.36; N 19.60.

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