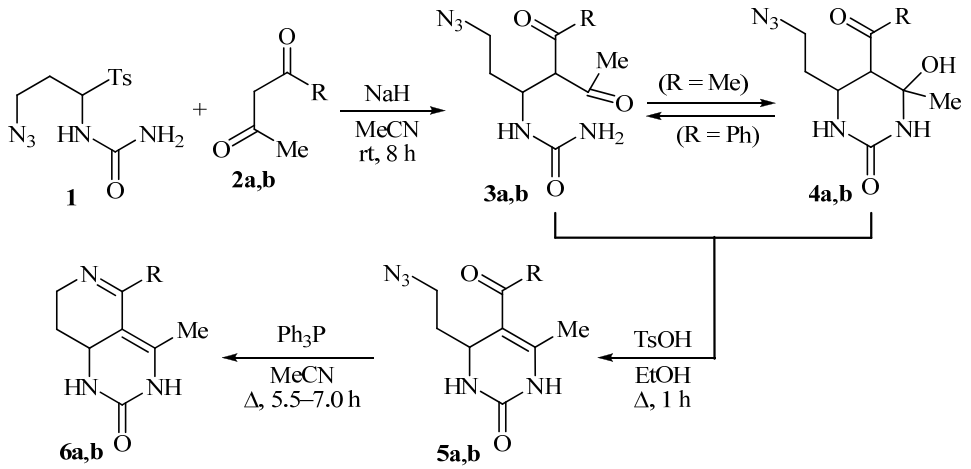
ПИСЬМА В РЕДАКЦИЮ

A NEW SYNTHESIS OF PYRIDO[4,3-*d*]PYRIMIDIN-2-ONES

Keywords: pyrido[4,3-*d*]pyrimidin-2-ones, 1,2,3,4-tetrahydropyrimidin-2-ones, amidoalkylation, aza-Wittig reaction, Staudinger reaction.

Pyrido[4,3-*d*]pyrimidines are of current interest due to their multifaceted pharmacological profiles. For example, they manifest remarkable inhibitory properties against epidermal growth factor receptor tyrosine kinase [1] and dihydrofolate reductase [2]. A significant number of methods for the preparation of pyrido[4,3-*d*]pyrimidines have been reported so far in the literature (for reviews, see [3, 4]). However, these methods do not include intramolecular aza-Wittig reaction, which is widely used today for nitrogen heterocycles' ring construction (for reviews, see [5, 6]). Herein, we describe our preliminary results on the preparation of previously unknown hexahydropyrido[4,3-*d*]pyrimidine-2-ones using Staudinger – aza-Wittig reaction of 5-acyl-4-(2-azidoethyl)-3,4-dihydropyrimidin-2(1*H*)-ones mediated by PPh_3.

Readily available *N*-(3-azido-1-tosylpropyl)urea (**1**) was used as a starting material. This compound was prepared by three-component condensation of 3-azidopropanal, *p*-toluenesulfinic acid and urea in water [7]. The reaction of urea **1** with the Na-enolate of acetylacetone (**2a**) in MeCN afforded hydroxypyrimidine **4a** [7], which was dehydrated in the presence of TsOH (EtOH, reflux, 1 h) to give tetrahydropyrimidine **5a** in 77% yield.



a R = Me, **b** R = Ph

In contrast, the reaction of urea **1** with the Na-enolate of benzoylacetone (**2b**) (MeCN, rt, 8 h) resulted in acyclic *N*-(oxoalkyl)urea **3b** as a 48:52 mixture of two diastereomers in 79% yield. We suppose that cyclization of urea **3b** into pyrimidine **4b** does not proceed due to steric hindrance from the benzoyl group. Acid-catalyzed

heterocyclization/dehydration of urea **3b** (TsOH, EtOH, reflux, 1 h) gave compound **5b** in 89% yield.

The prepared pyrimidinones **5a**,**b** reacted with PPh_3 (1.1 equiv) in refluxing MeCN for 5.5–7.0 h to afford the target pyrido[4,3-*d*]pyrimidines **6a**,**b** in 94–95% yields as a result of Staudinger – intramolecular aza-Wittig reaction.

We envisage that the described method for the preparation of pyrido[4,3-*d*]-pyrimidine scaffold is very promising since both the components of the amidoalkylation reaction can be widely varied. In particular, various *N*-(3-azido-1-tosylpropyl)ureas can be prepared using readily available β-azidoaldehydes bearing substituents at the α- and/or β-positions. Furthermore, the prepared hexahydropyrido[4,3-*d*]pyrimidin-2-ones can be aromatized or reduced by routine procedures expanding the synthetic utility of the method.

IR spectra in nujol were recorded on a Bruker Vector 22 spectrophotometer. Band characteristics in the IR spectra are defined as very strong (vs), strong (s), medium (m), and weak (w). ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300 and 75 MHz, respectively) in DMSO-d_6, central signal of the solvent was used as the internal standard (2.50 ppm for ^1H nuclei, 39.5 ppm for ^{13}C nuclei). Elemental analysis was carried out on Thermo Finnigan Flash EA1112 apparatus. Melting points were determined in open capillary tubes using an electric melting point apparatus with a calibrated thermometer (heating rate 1–2°C/min).

***N*-(1-Azido-4-benzoyl-5-oxohexan-3-yl)urea (3b)**. Dry MeCN (15 ml) was added to a mixture of benzoylacetone (**2b**) (1.539 g, 9.49 mmol) and NaH (0.224 g, 9.33 mmol), and the resulting suspension was stirred at room temperature for 40 min followed by addition of sulfone **1** (2.764 g, 9.30 mmol) and dry MeCN (9 ml). The suspension was stirred for 8 h, and the solvent was removed in vacuum. The residue was triturated with saturated aqueous $NaHCO_3$ (10 ml) and petroleum ether (15 ml), the obtained suspension was left overnight at room temperature, and cooled to 0°C. The precipitate was filtered, washed with ice-cold water and petroleum ether. The solid obtained was dried on the filter in a vacuum desiccator over P_2O_5, cooled to –10°C, washed with cold Et_2O (3 × 10 ml, –10°C), and dried to give urea **3b** as a mixture of two diastereomers (48:52). Yield 2.222 g (79%). An analytically pure sample as a diastereomeric mixture (52:48) was obtained by crystallization of the crude product from EtOH. White solid, mp 124.5–125.0°C (decomp.). IR spectrum, ν, cm^{-1}: 3420 (s), 3404 (s), 3366 (s), 3212 (br. s) (ν NH), 3087 (w) (ν CH Ar), 2151 (m), 2104 (vs) (ν N_3), 1717 (s), 1708 (s) (ν C=O), 1662 (s), 1651 (vs) (amide I), 1617 (m), 1610 (m), 1595 (m), 1578 (m) (ν CC Ar), 1542 (s), 1522 (s) (amide II), 771 (s), 697 (s) (δ CH Ar). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.01–7.94 (2H, m, H-2,6 Ph); 7.72–7.63 (1H, m, H-4 Ph); 7.60–7.50 (2H, m, H-3,5 Ph); 6.19 (0.52H, d, ^3J = 9.7, NH (major)); 6.05 (0.48H, d, ^3J = 9.6, NH (minor)); 5.65 (1.04H, s, NH_2 (major)); 5.59 (0.96H, s, NH_2 (minor)); 5.20 (0.52H, d, ^3J = 4.9, C<u>H</u>Ac (major)); 5.04 (0.48H, d, ^3J = 7.7, C<u>H</u>Ac (minor)); 4.56–4.43 (1H, m, C<u>H</u>NH); 3.43–3.22 (2H, m, CH_2N_3); 2.26 (1.56H, s, $COCH_3$ (major)); 2.13 (1.44H, s, $COCH_3$ (minor)); 1.82–1.56 (2H, m, C<u>H</u>$_2$$CH_2N_3$). Found, %: C 55.56; H 5.71; N 23.02. $C_{14}H_{17}N_5O_3$. Calculated, %: C 55.44; H 5.65; N 23.09.

5-Acetyl-4-(2-azidoethyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (5a). A solution of compound **4a** (1.737 g, 7.20 mmol) and $TsOH·H_2O$ (0.263 g, 1.38 mmol) in EtOH (20 ml) was refluxed for 1 h under stirring, and then the solvent was removed in vacuum. The oily residue was triturated with saturated aqueous $NaHCO_3$ (3 ml) and petroleum ether (10 ml), and the obtained suspension was cooled to 0°C. The precipitate was filtered, washed with ice-cold water and petroleum ether. The solid obtained was dried on the filter in a vacuum desiccator over P_2O_5, washed with cold Et_2O (3 × 5 ml, –10°C), and dried. Yield 1.231 g (77%), white solid, mp 150.0–150.5°C (decomp., MeCN). IR spectrum, ν, cm^{-1}: 3364 (w), 3230 (s), 3113 (s) (ν NH), 2172 (m), 2122 (m), 2095 (s) (ν N_3), 1713 (vs) (amide I), 1669 (s) (ν C=O), 1598 (s) (ν C=C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 9.05 (1H, br. d, ^4J = 1.9, 1-NH); 7.55 (1H, br. dd, ^3J

= 3.9, ^4J = 1.9, 3-NH); 4.20 (1H, ddd, ^3J = 7.8, ^3J = 4.1, ^3J = 3.9, 4-CH); 3.44–3.30 (2H, m, CH_2N_3); 2.21 (3H, s, $COCH_3$); 2.19 (3H, s, 6-CH_3); 1.67–1.49 (2H, m, $C\underline{H}_2CH_2N_3$). Found, %: C 48.40; H 5.86; N 31.47. $C_9H_{13}N_5O_2$. Calculated, %: C 48.42; H 5.87; N 31.37.

4-(2-Azidoethyl)-5-benzoyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (5b). Compound **5b** was prepared from urea **3b** (0.835 g, 2.75 mmol) and $TsOH\cdot H_2O$ (0.109 g, 0.57 mmol) in EtOH (13 ml) as described for pyrimidine **5a**. Yield 0.700 g (89%), slightly yellow solid, mp 186.0–186.5°C (decomp., EtOH). IR spectrum, ν, cm^{-1}: 3291 (br. vs), 3175 (br. m) (ν NH), 3056 (w) (ν CH Ar), 2100 (m), 2086 (s) (ν N_3), 1710 (s) (amide I), 1678 (vs), 1653 (m) (ν C=O), 1601 (s), 1591 (s), 1572 (s) (ν C=C, ν CC Ar), 743 (s), 712 (m) (δ CH Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.10 (1H, br. d, ^4J = 1.9, 1-NH); 7.59–7.43 (6H, m, 3-NH, H Ph); 4.25 (1H, dt, ^3J = 6.0, ^3J = 3.7, 4-CH); 3.44–3.31 (2H, m, CH_2N_3); 1.68 (2H, ddd, ^3J = 7.2, ^3J = 6.6, ^3J = 6.0, $C\underline{H}_2CH_2N_3$); 1.61 (3H, s, CH_3). Found, %: C 58.89; H 5.57; N 23.95. $C_{14}H_{15}N_5O_2\cdot 0.07C_2H_5OH$. Calculated, %: C 58.86; H 5.39; N 24.27.

4,5-Dimethyl-3,7,8,8a-tetrahydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (6a). Dry MeCN (6 ml) was added to a mixture of pyrimidine **5a** (0.537 g, 2.41 mmol) and PPh_3 (0.689 g, 2.63 mmol), and the obtained mixture was refluxed under stirring for 5.5 h. A clear solution formed at the beginning of reflux, and after 10 min the product precipitated to give a suspension. After the reaction was complete, the mixture was cooled to –10°C, the precipitate was filtered on a cold filter (–10°C), washed with cold MeCN (4 × 2 ml, –10°C), Et_2O (5 ml, 5°C), and dried. Yield 0.407 g (94%), white solid, mp 229.5°C (decomp.; EtOH). IR spectrum, ν, cm^{-1}: 3213 (s), 3105 (s), 3082 (s) (ν NH), 1692 (vs) (amide I), 1639 (s) (ν C=C), 1593 (s) (ν C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.42 (1H, br. s, 3-NH); 7.01 (1H, s, 1-NH); 3.99 (1H, ddq, ^3J = 10.8, ^3J = 4.8, ^5J = 1.4, 8a-CH); 3.57–3.47 (1H, m, 7-CH*eq*); 3.35–3.22 (1H, m, 7-CH*ax*); 2.13 (3H, dd, ^5J = 2.0, ^5J = 1.1, 5-CH_3); 2.05 (3H, d, ^5J = 1.4, 4-CH_3); 1.88–1.80 (1H, m, 8-H*eq*); 1.47–1.34 (1H, m, 8-H*ax*). ^{13}C NMR spectrum, δ, ppm: 160.3 (C-5); 154.3 (C-2); 137.4 (C-4); 104.2 (C-4a); 48.8 (C-8a); 46.5 (C-7); 29.3 (C-8); 28.1 (5-CH_3); 18.6 (4-CH_3). Found, %: C 60.12; H 7.30; N 23.58. $C_9H_{13}N_3O$. Calculated, %: C 60.32; H 7.31; N 23.45.

4-Methyl-5-phenyl-3,7,8,8a-tetrahydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (6b). A solution of pyrimidine **5b** (0.507 g, 1.78 mmol) and PPh_3 (0.529 g, 2.02 mmol) in dry MeCN (40 ml) was refluxed for 7 h under stirring, and then the solvent was removed in vacuum. The residue was purified by column chromatography on silica gel 60 (17 g) eluting with $CHCl_3$–MeOH (from 100:0 to 20:1). Yield 0.403 g (95%), slightly yellow crystals, mp 197.0–197.5°C (decomp., MeCN). IR spectrum, ν, cm^{-1}: 3188 (s), 3127 (s), 3086 (s), 3060 (s) (ν NH), 1717 (vs) (amide I), 1645 (s) (ν C=C), 1584 (m) (ν CC Ar), 1557 (s) (ν C=N), 1491 (m) (ν CC Ar), 705 (s) (δ CH Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.53 (1H, br. s, 3-NH); 7.05 (1H, s, 1-NH); 7.48–7.34 (5H, m, H Ph); 4.14 (1H, ddq, ^3J = ^3J = 5.8, ^5J = 1.4, 8a-CH); 3.82–3.73 (1H, m) and 3.37–3.28 (1H, m, 7-CH_2); 1.81–1.61 (2H, m, 8-CH_2); 1.30 (3H, d, ^5J = 1.4, 4-CH_3). ^{13}C NMR spectrum, δ, ppm: 165.7 (C-5); 154.0 (C-2); 141.4 (C-*i* Ph); 136.3 (C-4); 128.9 (C-4 Ph); 128.2 (C-3,5 Ph); 127.5 (C-2,6 Ph); 103.1 (C-4a); 47.6 (C-8a); 47.3 (C-7); 31.6 (C-8); 17.8 (CH_3). Found, %: C 69.49; H 6.33; N 17.41. $C_{14}H_{15}N_3O$ Calculated, %: C 69.69; H 6.27; N 17.41.

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