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CONVENIENT APPROACH TO THE SYNTHESIS OF PYRIMIDO[5',4':4,5]PYRROLO[2,4-*c*][1,4]OXAZINE, A NEW HETEROCYCLIC SYSTEM

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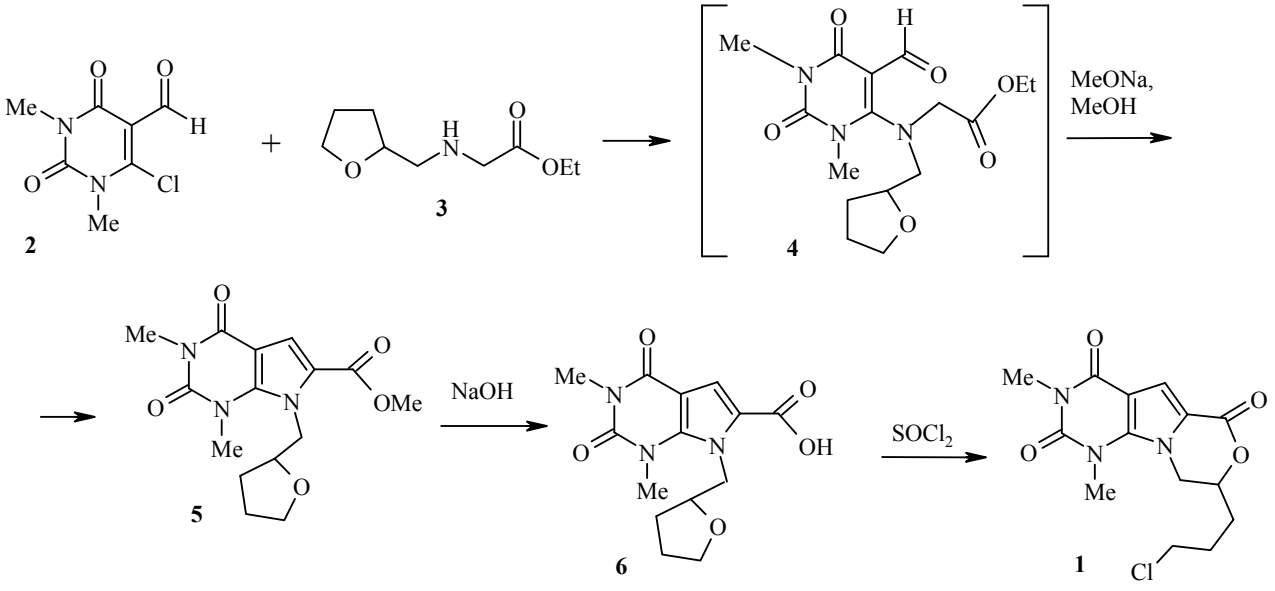
The promise of new condensed heterocyclic systems containing the 1,3-dimethyluracil pharmacophoric fragment primarily accounts for the search for new approaches to the synthesis of such compounds, which display pronounced physiological activity [1-5]. We have developed a convenient method for the preparation of a representative of a new heterocyclic system, namely, pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine **1**.

The reaction of chloro aldehyde **2** with the ethyl ester of N-tetrahydrofurfurylaminoacetic acid (**3**) under mild conditions involves replacement of the labile chlorine atom by a tetrahydrofurfurylglycine residue to give ester **4**. Treatment of ester **4** with sodium methylate in absolute methanol leads to intramolecular cyclization



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accompanied by transesterification and formation of the methyl ester of pyrrolo[2,3-*d*]pyrimidine-6-carboxylic acid (**5**). Hydrolysis of ester **5** gives acid **6**, which recyclizes by the action of thionyl chloride at 80°C to give a derivative of pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine **1**. This can be possible due to good arrangement of a tetrahydrofuran unit and a carboxyl group.

The ^{1}H NMR spectra were taken on a Varian Unian Plus spectrometer at 400 MHz in DMSO-d_6 with TMS as the internal standard. The IR spectra were taken on a Bruker Vertex 70 FTIR for KBr pellets. The chemical ionization mass spectra were taken on an Agilent 1100 liquid chromatography/mass selective detector.

Methyl Ester of 1,3-Dimethyl-2,4-dioxo-7-[(2-tetrahydrofuryl))methyl]-2,3,4,7-tetrahydro-1H-pyrrolo-[2,3-*d*]pyrimidine-6-carboxylic Acid (5). A mixture of ester **3** (1.85 g, 1 mmol) and triethylamine (1.4 ml, 1 mmol) in benzene (7.5 ml) was added dropwise with stirring and cooling to 0-5°C to a suspension of aldehyde **2** (2 g, 1 mmol) in benzene (8 ml). The reaction mixture was maintained for 12 h at room temperature. The precipitate of triethylamine hydrochloride was filtered off. The filtrate was evaporated and the residue was dissolved in methanol (15 ml). Then, sodium methylate (0.53 g, 1 mmol) in methanol (4 ml) was added dropwise. The reaction mixture was maintained for 3 h at room temperature. The precipitate formed was filtered off and washed with water (10 ml) to give 1.72 g (54%) ester **5**; mp 150-152°C (ethanol). IR spectrum, ν, cm^{-1}: 1691 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.50 (1H, m, CH); 1.79 (2H, m, CH_2); 1.96 (1H, m, CH); 3.23 (3H, s, NCH_3); 3.58 (1H, m, CH); 3.67 (1H, m, CH); 3.73 (3H, s, NCH_3); 3.77 (3H, s, OCH_3); 3.96 (1H, m, CH); 4.76 (1H, m, CH); 4.87 (1H, m, CH); 7.23 (1H, s, CH). Mass spectrum, *m/z*: 322 $[M+H]^+$. Found, %: C 56.12; H 6.03; N 12.08. $C_{15}H_{19}N_3O_5$. Calculated, %: C 56.07; H 5.96; N 13.08.

1,3-Dimethyl-2,4-dioxo-7-[(2-tetrahydrofuryl)methyl]-2,3,4,7-tetrahydro-1-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic Acid (6). Sodium hydroxide (0.22 g. 5.5 mmol) was added to a suspension of ester **5** (1.6 g, 5 mmol) in 10 ml 40% aqueous ethanol and heated until dissolved at 60°C. The solution formed was maintained for 30 min. The reaction mixture was then cooled and neutralized by adding acetic acid. The precipitate formed was filtered off and washed with water (30 ml) to give 0.64 g (42%) acid **6**; mp 209-211°C (ethanol). IR spectrum, ν, cm^{-1}: 1643 (C=O), 1691 (C=O). NMR spectrum, δ, ppm: 1.49 (1H, m, CH); 1.76 (2H, m, CH_2); 1.93 (1H, m, CH); 3.21 (3H, s, NCH_3); 3.56 (1H, m, CH); 3.64 (1H, m, CH); 3.71 (3H, s, NCH_3); 3.95 (1H, m, CH); 4.77 (1H, m, CH); 4.89 (1H, m, CH); 7.18 (1H, s, CH); 12.66 (1H, br. s, OH). Mass spectrum, *m/z*: 308 $[M+H]^+$. Found, %: C 54.78; H 5.62; N 12.41. $C_{14}H_{17}N_3O_5$. Calculated, %: C 54.72; H 5.58; N 13.67.

8-(3-Chloropropyl)-1,3-dimethyl-8,9-dihydro-2H-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine-2,4,6(1H,3H)-trione (1). A suspension of acid **6** (0.92 g, 3 mmol) in thionyl chloride (2 ml) was heated to reflux. The solution formed was heated for 20 min at 100°C. The precipitate formed was filtered off and washed with benzene (10 ml) in ethanol (10 ml) to give 0.66 g (67%) trione **1**; mp 219-221°C (DMF). IR spectrum, ν, cm^{-1}: 1661 (C=O), 1689 (C=O), 1722 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.91 (4H, m, $2CH_2$); 3.22 (3H, s, NCH_3); 3.68 (3H, s, NCH_3); 3.74 (2H, m, CH_2); 4.28 (1H, m, CH); 4.73 (1H, m, CH); 4.84 (1H, m, CH); 7.26 (1H, s, CH). Mass spectrum, *m/z*: 326 $[M+H]^+$. Found, %: C 51.81; H 5.05; Cl 10.95; N 12.80. $C_{14}H_{16}ClN_3O_4$. Calculated, %: C 51.62; H 4.95; Cl 10.88; N 12.90.

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