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NOVEL METHOD FOR SYNTHESIS OF PYRIDO[4,3-*d*]PYRIMIDINES

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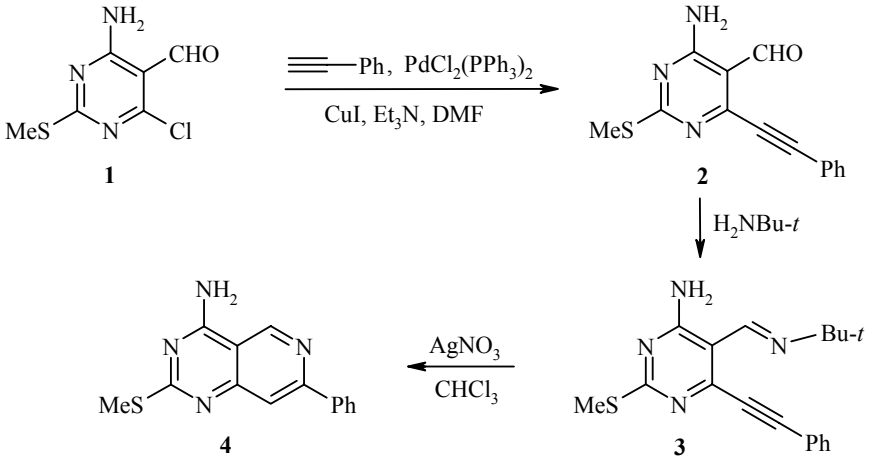
Recently we synthesized some alkynyl derivatives of pyrimidine and pyrrolo[2,3-*d*]pyrimidine, and we showed that they can be used to obtain pyrrolo[3,2-*d*]pyrimidine 7-oxides [1, 2] and pyrrolo[2,3,4-*de*]-pyrimido[5',4':5,6][1,3]diazepino[1,7-*a*]indoles [3] respectively. Continuing our research in this direction, in this report we present a novel route for synthesis of a pyrido[4,3-*d*]pyrimidine heterocyclic system using 4-amino-6-chloro-2-methylthiopyrimidine-5-carbaldehyde (**1**) as the starting compound. Interest in methods for synthesis of pyrido[4,3-*d*]pyrimidine derivatives to a significant extent is due to the biological activity of these compounds [4-6].

We synthesized phenylethynylpyrimidine **2** by means of the palladium-catalyzed reaction of cross coupling compound **1** with phenylacetylene. The reaction was carried out under an argon atmosphere at a temperature of 50-60°C, using 4 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, and a 3-fold molar excess of phenylacetylene.



Heating aldehyde **2** with excess *tert*-butylamine in an autoclave at 100°C leads to formation of imine **3** in 93% yield. Preliminary study of the reaction of cyclization of compound **3** to form the corresponding pyrido[4,3-*d*]pyrimidine **4** in the presence of Cu(I) or Ag(I) salts showed that $AgNO_3$ is an effective catalyst for this conversion. Compound **4** was synthesized in 79% yield by heating phenylethynylpyrimidine **3** in chloroform in the presence of 10 mol % $AgNO_3$.

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The IR spectra were taken in vaseline oil on an FT-IR Spectrum BX II (Perkin-Elmer) spectrophotometer. The ^{1}H NMR spectra were obtained on a Varian INOVA (300 MHz) spectrometer using TMS as an internal standard. The course of the reactions and the purity of the compounds obtained were followed by TLC on Alufol Silica Gel 60 F254 plates (Merck).

The starting 4-amino-6-chloro-2-methylthiopyrimidine-5-carbaldehyde (**1**) was synthesized according to the method in [7].

4-Amino-2-methylthio-6-(phenylethynyl)pyrimidine-5-carbaldehyde (2). Yield 42%; mp 178-179°C (octane). IR spectrum (vaseline oil), ν, cm^{-1}: 3381, 3277 (NH_2), 2214 (C≡C), 1765 (CHO). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 2.59 (3H, s, SCH_3); 5.84 (1H, br. s, NH); 7.43-7.67 (5H, m, ArH); 8.60 (1H, br. s, NH); 10.49 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 14.6, 98.4, 108.8, 120.9, 130.6, 132.8, 155.1, 160.9, 177.6, 191.7. Mass spectrum, *m*/*z* (%): 269 $[M]^+$ (100). Found, %: C 62.69; H 4.15; N 15.75. $C_{14}H_{11}N_3OS$. Calculated, %: C 62.43; H 4.12; N 15.60.

4-Amino-5-*tert*-butyliminomethyl-2-methylthio-6-(phenylethynyl)pyrimidine (3). Yield 93%; mp 109-110°C (2-PrOH–H_2O). IR spectrum (vaseline oil), ν, cm^{-1}: 3445, 3269 (NH_2), 2214 (C≡C). ^{1}H NMR spectrum (300 MHz, $(CD_3)_2CO$), δ, ppm: 1.36 (9H, s, $3CH_3$); 2.58 (3H, s, SCH_3); 5.70 (1H, br. s, NH); 7.53-7.71 (5H, m, ArH); 8.94 (1H, s, CH); 10.06 (1H, br. s, NH). Found, %: C 66.71; H 6.28; N 17.23. $C_{18}H_{20}N_4S$. Calculated, %: C 66.64; H 6.21; N 17.27.

4-Amino-2-methylthio-7-phenylpyrido[4,3-*d*]pyrimidine (4). Yield 79%; mp 144-145°C (toluene–octane). IR spectrum (vaseline oil), ν, cm^{-1}: 3402, 3388 (NH_2). ^{1}H NMR spectrum (300 MHz, CD_2Cl_2), δ, ppm: 2.58 (3H, s, SCH_3); 6.73 (2H, br. s, NH_2); 7.27 (1H, s, CH); 7.37-7.67 (5H, m, ArH); 8.89 (1H, s, CH). Found, %: C 62.69; H 4.58; N 20.79. $C_{14}H_{12}N_4S$. Calculated, %: C 62.66; H 4.51; N 20.88.

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