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UNEXPECTED REACTIONS OF 4-AMINO-2-METHYLSULFONYL-5-NITRO-6-PHENYL-ETHYNYLPYRIMIDINE WITH NUCLEOPHILES

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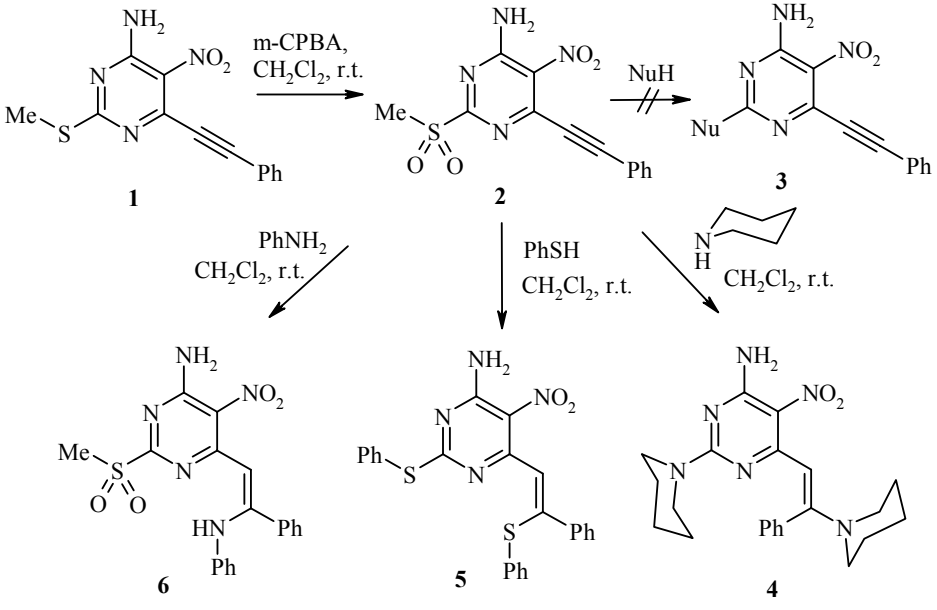
Recently, we have reported that 4-amino-6-arylethynyl-5-nitropyrimidines in dry pyridine undergo smooth intramolecular cyclization to give pyrrolo[3,2-*d*]-pyrimidine 5-oxides [1, 2]. The latter compounds, being aza-analogues of isatogens, attracted our attention as potential traps for free radicals in biological milieu [3–5]. In continuing our research aimed on the synthesis of polysubstituted pyrrolo-[3,2-*d*]pyrimidine 5-oxides *via* cyclization of 6-arylethynyl-5-nitropyrimidines, we decided to perform modification of the 2-position of the starting 6-arylethynyl-5-nitropyrimidines based on oxidation of methylthio moiety followed by nucleophilic substitution reaction. Thus, reaction of 4-amino-2-methylthio-5-nitro-6-phenylethynylpyrimidine (**1**) with excess of *m*-chloroperbenzoic acid in dihloromethane at room temperature provided the corresponding 4-amino-2-methylsulfonyl-5-nitro-6-phenylethynylpyrimidine (**2**) in 70% yield. Unfortunatelly, the reaction of compound **2** with some nucleophilic reagents did not lead to formation of 2-substituted 4-amino-5-nitro-6-phenylethynylpyrimidines **3**. We observed that C≡C bond of the title compound appeared to be more reactive towards nucleophiles than the C(2)–SO_2Me moiety of the pyrimidine ring.



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The reaction of compound **2** with 2 equivalents of piperidine or thiophenol in dichloromethane at room temperature furnished products **4** and **5**. However, when compound **2** was treated with a weaker nucleophile (aniline) only addition reaction to the triple bond was observed. It should be noted that addition reactions of nucleophiles to the C≡C bond of the title compounds are regio- and stereoselective, as we have shown recently [6]. So these reactions lead to the formation of *syn*-addition (in the case of secondary amine) or *anti*-addition (in the case of thiophenol or primary amine) products **4**–**6**, respectively.

The IR spectra were obtained on a Spectrum BX II FT-IR spectrophotometer (Perkin–Elmer) in KBr disks. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova (300 and 75 MHz respectively) internal standard TMS.

The starting 4-amino-2-methylthio-5-nitro-6-phenylethynylpyrimidine (**1**) was synthesized according to the method described in [6].

4-Amino-2-methylsulfonyl-5-nitro-6-phenylethynylpyrimidine (**2**). To a solution of compound **1** (0.5 g, 1.7 mmol) in dichloromethane (25 ml) *m*-chloroperbenzoic acid (0.83 g, 4.8 mmol) was added portion-wise. The resulting solution was stirred for 6 h at room temperature The precipitate was filtered off, washed with $NaHCO_3$ (sat.), and dried. The obtained compound **2** was pure and used in the next steps without further purification. Yield 70%; mp 202-205°C. IR spectrum, δ, cm^{-1}: 3447, 3288 (NH_2), 2205 (C≡C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.35 (3H, s, SO_2CH_3); 7.58-7.63 (3H, m, ArH); 7.73-7.79 (2H, m, ArH); 8.44 (2H, br. s, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 43.8, 83.9, 100.3, 119.8, 128.4, 130.5, 132.2, 144.5, 156.6, 164.7, 175.7. Found, %: C 49.49; H 3.34; N 17.39. $C_{13}H_{10}N_4O_4S$. Calculated, %: C 49.05; H 3.17; N 17.60.

Reaction of 4-Amino-2-methylsulfonyl-5-nitro-6-phenylethynylpyrimidine (**2**) **with Nucleophiles.** To a solution of compound **2** (0.32 g, 1 mmol) in dichloromethane (5 ml), the corresponding nucleophile (2 mmol) was added. The reaction mixture was kept at room temperature for 2 h. The solvent was evaporated under reduced pressure, the residue was recrystallized from 2-propanol to give compounds **4**, **5** or **6**.

4-Amino-5-nitro-6-[(*E*)-2-phenyl-2-(1-piperidinyl)ethenyl]-2-piperidinylpyrimidine (**4**). Yield 85%; mp 155-157°C. IR spectrum, δ, cm^{-1}: 3468, 3360 (NH_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 (4H, br. s, 2(CH_2)$_2$); 1.47 (4H, br. s, (CH_2)$_2$); 1.65 (4H, br. s, (CH_2)$_2$); 2.65 (2H, br. s, NCH_2); 3.19 (4H, br. s, N(CH_2)$_2$); 3.53 (2H, br. s, NCH_2); 6.51 (1H, s, CH); 7.32-7.36 (5H, m, ArH); 8.49 (2H, br. s, NH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.7, 24.8, 26.2, 26.3, 49.8, 50.2, 100.9, 117.9, 128.4, 128.6, 129.5, 138.6, 156.9, 159.8, 162.4, 163.8. Found, %: C 64.98; H 7.03; N 20.28. $C_{22}H_{28}N_6O_2$. Calculated, %: C 64.68; H 6.91; N 20.57.

4-Amino-5-nitro-6-[(*Z*)-2-phenyl-2-(phenylthio)ethenyl]-2-phenylthiopyrimidine (**5**). Yield 52%; mp 145-147 °C. IR spectrum, δ, cm^{-1}: 3450, 3368 (NH_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.00-7.04 (5H, m, ArH); 7.09-7.12 (3H, m, ArH); 7.30-7.35 (2H, m, ArH); 7.31 (1H, s, CH); 7.40-7.44 (3H, m, ArH); 7.67-7.69 (2H, m, ArH); 8.69 (2H, br. s, NH_2). Found, %: C 62.91; H 4.01; N 12.44. $C_{24}H_{18}N_4O_2S_2$. Calculated, %: C 62.86; H 3.96; N 12.22.

4-Amino-2-methylsulfonyl-5-nitro-6-[(*Z*)-2-phenyl-2-(phenylamino)ethenyl]pyrimidine (**6**). Yield 80%; mp 225-227°C. IR spectrum, δ, cm^{-1}: 3446, 3360, 3161 (NH_2, NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.28 (3H, s, SO_2CH_3); 6.30 (1H, s, CH); 6.77 (2H, d, *J* = 7.8, ArH); 6.98 (1H, t, *J* = 7.8, ArH); 7.13 (2H, d, *J* = 7.8, ArH); 7.42 (5H, s, ArH); 8.49 (2H, br. s, NH_2); 12.80 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm.: 43.8, 120.2, 121.6, 123.3, 127.7, 128.2, 128.3, 129.4, 136.4, 138.9, 157.9, 159.2, 162.1, 174.9. Found, %: C 56.58; H 4.53; N 16.16. $C_{20}H_{20}N_5O_4S$. Calculated, %: C 56.33; H 4.73; N 16.42.

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