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General Synthesis of 4-Aryloxy-6-methylpyrimidin-2-amines and Their Fragmentation under Positive Electrospray Ionization

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Abstract—A number of 4-aryloxy-6-methylpyrimidin-2-amines were synthesized by reaction of 2-amino-6-methylpyrimidin-4-yl 4-methylbenzenesulfonate with phenols. The main fragmentation pathway of these compounds under positive electrospray ionization is decomposition of the heterocycle.

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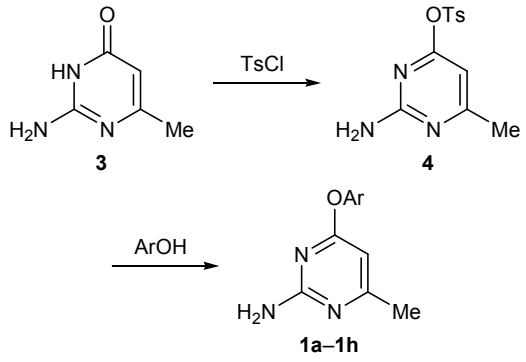
Up to now, no general method has been proposed for the synthesis of 4-aryloxy-6-methylpyrimidin-2-amines **1** that are structural analogs of biologically active 4-aryloxypyrimidin-2-amines [1] and 4-arylamino-6-methylpyrimidin-2-amines [2]. Some representatives were obtained by reaction of 6-chloro-4-methylpyrimidin-2-amine (**2**) with phenol [3] and 4-chlorophenol [4] in the presence of potassium hydroxide at ~100°C, as well as by treatment of **2** with phenol and naphthalen-1-ol at 165°C under microwave activation [5]. 6-(2-Methoxyphenoxy)-4-methylpyrimidin-2-amine was synthesized in less than 10% yield by reaction of **2** with 2-methoxyphenol in boiling toluene in the presence of metallic sodium [6].

The above procedures for the synthesis of compounds **1** require fivefold excess of phenols; furthermore, they involve the necessity of preparing intermediate chloro derivative **2** by reaction of 2-amino-6-methylpyrimidin-4(3*H*)-one (**3**) with highly toxic phosphoryl chloride [7] or its mixture with phosphorus pentachloride [8]. In the latter case, the chlorination of **3** gives mainly *N*-(6-methyl-4-chloropyrimidin-2-yl)-phosphoramidic dichloride [9].

In order to avoid the aforesaid difficulties in the synthesis of aminopyrimidines **1**, we tried an alternative approach based on the reaction of phenols with 2-amino-6-methylpyrimidin-4-yl 4-methylbenzenesulfonate (**4**). As a result, we isolated a series of aryloxypyrimidinamines **1a**–**1h** (Scheme 1). Replacement of the halogen atom in 2-chloro-4,6-dimethoxypyrimidine by methanesulfonyloxy group greatly activated the substrate to nucleophilic substitution in reactions with salicylic acid esters, and the corresponding products were obtained in up to 77% yield [10].

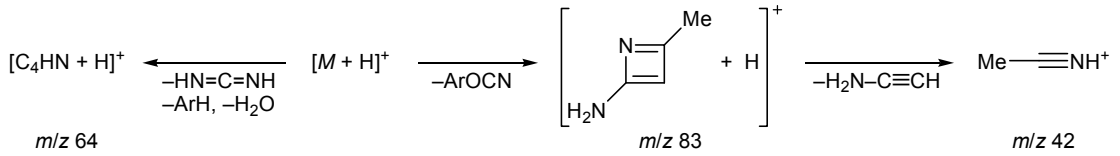
The electrophilicity of C^4 in molecule **4** is higher than in **2**; the charge on C^4 in **4** and **2** was estimated at +0.414 and +0.329, respectively. Compound **4** was synthesized by reaction of **3** with *p*-toluenesulfonyl chloride in 5% aqueous sodium hydroxide at a temperature not exceeding 15–20°C. The ^{1}H NMR spectrum of **4** contained a two-proton singlet at δ 6.9 ppm due to NH_2 group, and in the IR spectrum of **4** we observed absorption bands at 1379 and 1190 cm^{-1} typical of O–SO_2 group [11]. These data confirmed sulfonylation of the oxygen atom in **4**.

Scheme 1.



Ar = Ph (**a**), 4-EtC_6H_4 (**b**), 2-FC_6H_4 (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-IC_6H_4 (**f**), 3,4-$Me_2C_6H_3$ (**g**), 2,4-$Cl_2C_6H_3$ (**h**).

Scheme 2.



Published data on the *O*-mesylation of **3** are contradictory [12, 13]. According to [13], the reaction of **3** with 4-bromobenzenesulfonyl chloride under analogous conditions afforded 2-amino-6-methylpyrimidin-4-yl 4-bromobenzenesulfonate (**5**). Recrystallization of **5** from propan-2-ol gave 2-amino-6-methyl-4-oxo-3,4-dihydropyrimidinium 4-bromobenzenesulfonate, presumably due to partial hydrolysis of **5** with water present in the solvent.

To prevent hydrolysis, compound **4** was recrystallized from a mixture of anhydrous benzene and cyclohexane, but the yield of pure **4** did not exceed 30%. We succeeded in improving the yield by 15–20% by Soxhlet extraction of **4** with a minimum amount of the same solvent system instead of recrystallization.

The reactions of **4** with phenols, including *ortho*-substituted ones, were carried out by heating equimolar amounts of the reactants at 140°C without a solvent or catalyst. These conditions ensured homogeneity of the melt. After cooling, the solid product was treated with 10% aqueous sodium hydroxide. Chromatographically pure aryloxypyrimidines **1a**–**1h** were thus isolated in 45–83% yield.

The structure of **1a**–**1h** was confirmed by ^{1}H NMR and mass spectra. Compounds **1a**–**1h** displayed in the ^{1}H NMR spectra signals from the methyl group at δ 2.2 ppm, amino group at δ 6.3–6.5 ppm, and aromatic protons in the region δ 6.8–7.7 ppm. The mass spectra of **1a**–**1h** (positive electrospray ionization) contained $[M + H]^+$ ion peaks. Compounds **1a**–**1c** and **1g** also displayed peaks of doubly protonated molecular ions $[M + 2H]^{2+}$. A characteristic feature of all aryloxypyrimidines **1a**–**1h** is the presence in their mass spectra of three fragment ion peaks with *m*/*z* 83, 64, and 42, originating from decomposition of the heterocycle. An exception was compound **1c** which showed a low-intense ion peak with *m*/*z* 202 (I_{rel} <5%) resulting from elimination of hydrogen fluoride from the $[M + 2H]^{2+}$ ion. A probable scheme of pyrimidine ring fragmentation includes the formation of $[MeCN + H]^+$ ion (*m*/*z* 42) via decomposition of intermediate 4-methylazet-2-aminium ion (*m*/*z* 83) (Scheme 2). Less probable fragmentation of the pyrimidine ring in **1a**–**1h** implies elimination of several neutral species, including the corresponding arene, from $[M + H]^+$ with formation of $[C_4HN + H]^+$ (*m*/*z* 64).

Thus, the reaction of 2-amino-6-methylpyrimidin-4-yl 4-methylbenzenesulfonate with phenols may be regarded as a general method for the synthesis of 4-aryloxy-6-methylpyrimidin-2-amines.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance III-400 spectrometer at 400 MHz using DMSO-d_6 as solvent; the chemical shifts were measured relative to the residual proton signal of the solvent. The IR spectrum of **4** was taken in KBr on a Shimadzu FTIR-8400S spectrometer. The mass spectra were obtained on a Waters XEVO TQD tandem quadrupole mass spectrometer (positive electrospray ionization, capillary voltage 2 kV, ion source temperature 150°C) coupled with a Waters Acquity UPLC liquid chromatograph (Acquity UPLC BEH C18 column, 2.1 × 100 mm; temperature 35±1°C; eluent acetonitrile–2% formic acid). The elemental compositions were determined on a Leco CHNS-932 analyzer. The purity of the isolated compounds was checked by TLC on Sorbfil PTSKh-AF-V-UF plates using acetone–hexane (1 : 1, A) or butan-1-ol–acetic acid–water (1 : 1 : 1, B) as eluent; spots were visualized under UV light (λ 254 nm). The charges on atoms in molecules **2** and **4** were calculated according to the extended Hückel approximation (ChemDraw Ultra 11.0).

4-Aryloxy-6-methylpyrimidin-2-amines 1a–1h (*general procedure*). A mixture of 0.6 g (2.1 mmol) of *p*-toluenesulfonate **4** and 2.1 mmol of the corresponding phenol was heated for 1 h at 140°C. The melt was cooled and thoroughly ground with 10% aqueous sodium hydroxide. The undissolved material was filtered off, washed with water, and dried at 70°C until constant weight. Analytical samples were obtained by recrystallization from appropriate solvent, followed by drying at 70°C until constant weight.

4-Methyl-6-phenoxypyrimidin-2-amine (1a). Yield 0.29 g (67%), mp 201°C (from cyclohexane–

benzene, 1:2); published data [3]: mp 194–195°C; R_f 0.49 (A). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, Me), 5.94 s (1H, CH), 6.46 s (2H, NH_2), 7.11–7.44 m (5H, Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 202.06 (77) $[M + H]^+$, 203.12 (13) $[M + 2H]^{2+}$, 83.01 (49), 63.91 (3), 42.05 (100). Found, %: C 65.27; H 5.65; N 20.57. $C_{11}H_{11}N_3O$. Calculated, %: C 65.66; H 5.51; N 20.88.

4-(4-Ethylphenoxy)-6-methylpyrimidin-2-amine (1b). Yield 0.22 g (45%), mp 196°C (from EtOH), R_f 0.56 (A). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, **Me**CH_2), 2.19 s (3H, Me), 2.64 q (MeC**H**$_2$), 5.89 s (1H, CH), 6.39 s (2H, NH_2), 7.00 d (2H, H_{arom}), 7.23 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 230.11 (100) $[M + H]^+$, 231.17 (33) $[M + 2H]^{2+}$, 83.07 (51), 63.97 (6), 42.05 (97). Found, %: C 67.67; H 6.46; N 18.19. $C_{13}H_{15}N_3O$. Calculated, %: C 68.10; H 6.59; N 18.33.

4-(2-Fluorophenoxy)-6-methylpyrimidin-2-amine (1c). Yield 0.31 g (66%), mp 186°C (from MeCN), R_f 0.87 (A). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, Me), 6.06 s (1H, CH), 6.45 s (2H, NH_2), 7.20–7.31 m (4H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 220.09 (85) $[M + H]^+$, 221.09 (15) $[M + 2H]^{2+}$, 202.06 (3), 83.01 (51), 64.03 (3), 42.05 (100). Found, %: C 59.89; H 4.63; N 18.79. $C_{11}H_{10}FN_3O$. Calculated, %: C 60.27; H 4.60; N 19.17.

4-(4-Chlorophenoxy)-6-methylpyrimidin-2-amine (1d). Yield 0.39 g (78%), mp 227°C (from H_2O–EtOH, 1:3); published data [4]: mp 220–221°C; R_f 0.53 (A). ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, Me), 6.00 s (1H, CH), 6.49 s (2H, NH_2), 7.16 d (2H, H_{arom}), 7.45 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 236.06 (78) $[M + H]^+$, 83.01 (50), 63.84 (4), 42.05 (100). Found, %: C 58.71; H 4.10; N 17.54. $C_{11}H_{10}ClN_3O$. Calculated, %: C 56.06; H 4.28; N 17.83.

4-(4-Bromophenoxy)-6-methylpyrimidin-2-amine (1e). Yield 0.47 g (78%), mp 242°C (from EtOH–DMF, 8:1), R_f 0.77 (A). ^{1}H NMR spectrum, δ, ppm: 2.21 s (3H, Me), 5.98 s (1H, CH), 6.44 s (2H, NH_2), 7.09 d (2H, H_{arom}), 7.56 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 280.00 (73) $[M + H]^+$, 83.07 (50), 63.97 (5), 42.05 (100). Found, %: C 46.67; H 3.75; N 14.81. $C_{11}H_{10}BrN_3O$. Calculated, %: C 47.17; H 3.60; N 15.00.

4-(4-Iodophenoxy)-6-methylpyrimidin-2-amine (1f). Yield 0.68 g (83%), mp 260°C (decomp., from (EtOH–DMF, 1:1), R_f 0.55 (A). ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, Me), 6.00 s (1H, CH), 6.48 s (2H, NH_2), 6.97 d (2H, H_{arom}), 7.73 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 327.99 (68) $[M + H]^+$, 83.07 (50), 63.97 (8), 42.05 (100). Found, %: C 40.02; H 2.78; N 12.39. $C_{11}H_{10}IN_3O$. Calculated, %: C 40.39; H 3.08; N 12.85.

4-(3,4-Dimethylphenoxy)-6-methylpyrimidin-2-amine (1g). Yield 0.37 g (75%), mp 239°C (from propan-2-ol), R_f 0.60 (A). ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, Me), 2.23 s (6H, Me), 5.88 s (1H, CH), 6.43 s (2H, NH_2), 6.81 d (1H, H_{arom}), 6.88 s (1H, H_{arom}), 7.14 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 230.17 (99) $[M + H]^+$, 231.11 (31) $[M + 2H]^{2+}$, 83.01 (49), 63.84 (5), 41.98 (96). Found, %: C 68.12; H 6.43; N 18.27. $C_{13}H_{15}N_3O$. Calculated, %: C 68.10; H 6.59; N 18.33.

4-(2,4-Dichlorophenoxy)-6-methylpyrimidin-2-amine (1h). Yield 0.47 g (81%), mp 202°C (from MeCN), R_f 0.71 (A). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, Me), 6.09 s (1H, CH), 6.50 s (2H, NH_2), 7.33 d (1H, H_{arom}), 7.46 d (1H, H_{arom}), 7.69 s (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 269.99 (92) $[M + H]^+$, 83.01 (52), 63.91 (7), 42.11 (100). Found, %: C 48.57; H 3.12; N 15.43. $C_{11}H_9Cl_2N_3O$. Calculated, %: C 48.91; H 3.36; N 15.56.

2-Amino-6-methylpyrimidin-4-yl 4-methylbenzenesulfonate (4). 2-Amino-6-methylpyrimidin-4(3*H*)-one (**3**) [14], 2 g (16 mmol), was dissolved in a 5% aqueous solution of sodium hydroxide (1 g), and 3.05 g (16 mmol) of *p*-toluenesulfonyl chloride was added in portions under vigorous stirring, maintaining the temperature at 15–20°C. The mixture was stirred for 3 h at that temperature, and the precipitate was filtered off, thoroughly washed with water, and dried in air until constant weight. The product was Soxhlet extracted with benzene–cyclohexane (2:1), the extract was cooled, and the precipitate was filtered off, washed with cyclohexane, and dried at 70°C until constant weight. Yield 2.08 g (46%), mp 142°C, R_f 0.56 (B). IR spectrum, ν, cm^{-1}: 1657 s (δNH_2), 1596 s, 1552 s (C=N, C=C), 1379 s, 1190 s (OSO_2). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, Me), 2.44 s (3H, Me), 6.15 s (1H, CH), 6.90 s (2H, NH_2), 7.47 d (2H, H_{arom}), 7.95 d (2H, H_{arom}). Found, %: C 51.72; H 4.24; N 14.71. $C_{12}H_{13}N_3O_3S$. Calculated, %: C 51.60; H 4.69; N 15.04.

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