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PALLADIUM-CATALYZED REACTION OF METHYL 5-AMINO-4-CHLORO-2-METHYLTHIOPYRROLO[2,3-*d*]-PYRIMIDINE-6-CARBOXYLATE WITH ARYLBORONIC ACIDS. SYNTHESIS OF 1,3,4,6-TETRAAZADIBENZO[*cd*,*f*]AZULENE HETEROCYCLIC SYSTEM

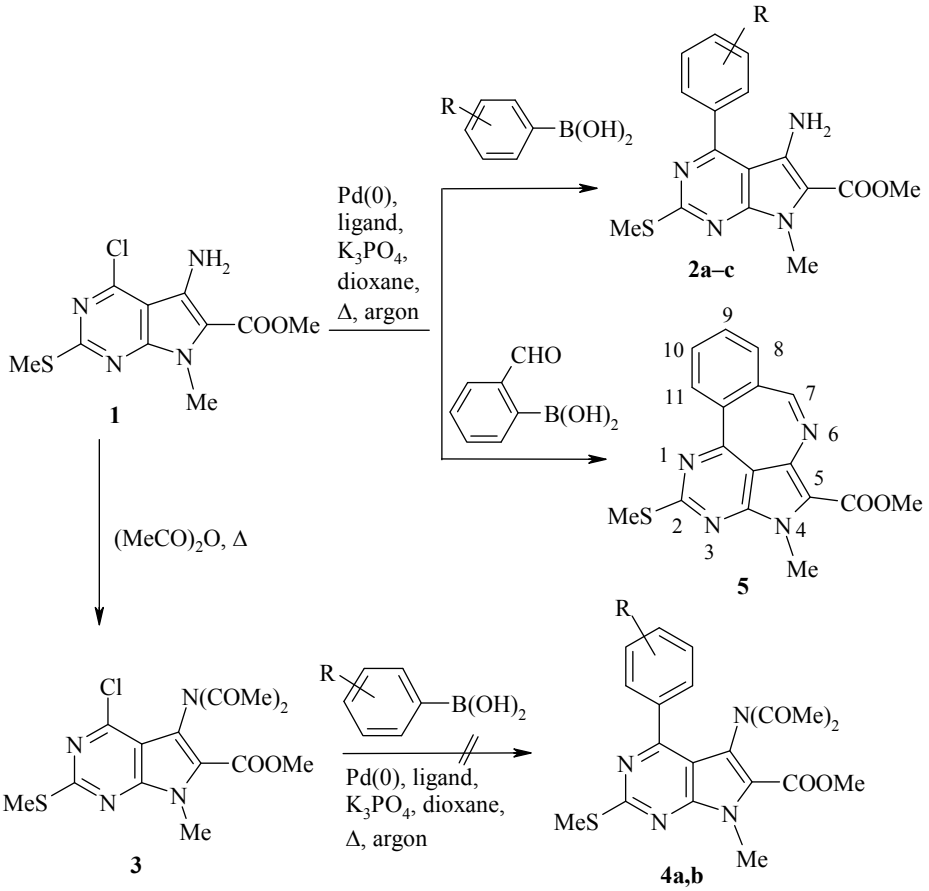
Densely substituted methyl 5-amino-4-aryl-7-methyl-2-methylthio-7H-pyrrolo[2,3-*d*]-pyrimidine-6-carboxylates were synthesized by the palladium-catalyzed cross-coupling reaction of methyl 5-amino-4-chloro-7-methyl-2-methylthio-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate with arylboronic acids using $Pd(OAc)_2$/dicyclohexyl(2-biphenyl)-phosphine/K_3PO_4 as a catalyst system. Reaction of methyl 5-amino-4-chloro-7-methyl-2-methylthio-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate with 2-formylphenylboronic acid led to a novel heterocyclic system – 1,3,4,6-tetraazadibenzo[*cd*,*f*]azulene.

Keywords: arylboronic acids, pyrrolo[2,3-*d*]pyrimidines, 1,3,4,6-tetraazadibenzo-[*cd*,*f*]azulene, palladium catalysis, Suzuki–Miyaura reaction.

Arylpurines are of particular importance due to anti-HCV, cytostatic, and antimycobacterial activities [1–4]. Arylpyrrolo[2,3-*d*]pyrimidines as isosters of biogenic purine, are often used as surrogates of purine bases and also many of them display interesting biological effects [5–11]. For their synthesis arylation reaction is a simple approach that does not involve the preparation of specific intermediates needed in the synthesis *via* cyclization procedures. In the past two decades, the Suzuki–Miyaura cross-coupling reaction has evolved into one of the most widely employed carbon-carbon bond forming processes including the preparation of biaryls [12–16]. However, despite the achieved advances in this area some difficulties and limitations still exist when nitrogen heterocycles are one or both of the coupling partners [17–22]. A literature survey on the arylpyrrolo[2,3-*d*]pyrimidines revealed that the Suzuki–Miyaura reaction in a pyrolo[2,3-*d*]pyrimidine series is explored insufficiently. To the best of our knowledge, few examples are reported on application of the palladium-catalyzed cross-coupling reaction for the arylation of a pyrrole ring of pyrrolo[2,3-*d*]pyrimidine [7, 23–27] and only two works have been recently published (one of them is from our laboratory) on arylation of a pyrimidine moiety of this heterocycle [28, 29]. In this context and continuing our studies on the synthesis of pyrimidine derivatives and related heterocycles [30–35], we present herein our results on the palladium-catalyzed cross-coupling reaction of the easily obtainable and versatile precursor of polycyclic heterocycles [31–33] – methyl 5-amino-4-chloro-7-methyl-2-methylthio-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (**1**) with selected arylboronic acids.

We initially conducted a brief screen of common palladium catalysts and

ligands using phenylboronic acid as the coupling partner of compound **1** in the Suzuki–Miyaura cross-coupling reaction. Performing the reaction of compound **1** with 1.2 eq. of phenylboronic acid using $PdCl_2(PPh_3)_2/K_3PO_4$ as a catalyst system in an anhydrous dioxane at the temperatures from ambient to reflux did not give the desired result. Only traces of compound **2a** were detected when the reaction was carried out at reflux temperature of dioxane for 10 h.



a R = H, **b** R = 4-(*t*-Bu), **c** R = 3,5-Cl_2

Using $Pd(OAc)_2/PPh_3/K_3PO_4$ as a catalyst system furnished the desired 4-phenylpyrrolopyrimidine **2a** in 30% yield (Scheme). However reaction of **1** with 4-*tert*-butylphenylboronic acid under these conditions gave a complex mixture of products, from which only negligible amount of compound **2b** was isolated. We supposed that the reason can be an interaction of the primary

amino group of compound **1** with boronic acids or palladium catalyst similar to that observed for 4-amino-2-chloropyrimidine [36]. To clarify an influence of

the 5-amino group of pyrrolo[2,3-*d*]pyrimidine on the cross-coupling reaction 5-diacetylamino derivative **3** was synthesized. However, compound **3** did not react with phenyl- or 4-*tert*-butylphenylboronic acids to give the desired compounds **4a**,**b** using $Pd(OAc)_2/PPh_3$, $PdCl_2(PPh_3)_2$, or $Pd(OAc)_2$/dicyclohexyl(2-biphenyl)phosphine as catalyst systems and K_3PO_4 as a base. In all cases initial compound **3** was recovered. Otherwise, catalytic system – $Pd(OAc)_2$/dicyclohexyl(2-biphenyl)phosphine/K_3PO_4 appeared to give the best results in the cross-coupling reaction of compound **1** with aryl boronic acids. Compounds **2b**,**c** were obtained in 80 and 64% yields, respectively. Reaction of compound **1** with 2-formylphenylboronic acid under the analogous conditions furnished a tetracyclic heterocycle – 1,3,4,6-tetraazadibenzo[*cd*,*f*]azulene. Structure assignment of compound **5** was based on IR, ^1H, ^{13}C NMR spectral and elemental analysis data. For example, in the IR spectrum of compound **5** there were no absorption bands for the amino group, which is observed in the IR spectra of **1** and **2a**–**c** in a region 3269–3453 cm^{-1}. The IR spectrum of compound **5** contain only one CO absorption band at 1702 cm^{-1}. It is shifted to a region of higher wavenumbers for *ca* 30 cm^{-1} in comparison with that of compounds **1**, **2a**–**c** containing the primary amino group capable to form intramolecular hydrogen bonds with the adjacent ester group. In the ^1H NMR spectrum of compound **5** along with other proton signals a singlet due to resonance of the CH=N group proton at 8.14 ppm is observed. The ^{13}C NMR spectrum of compound **5** is also consistent with the proposed structure.

In conclusion, the present investigation provides an access to a densely substituted 4-arylpyrrolo[2,3-*d*]pyrimidines that makes these compounds readily available for further chemical and biological study. The applied approach led to a novel *ortho*-, *peri*-fused heterocyclic system – 1,3,4,6-tetraazadibenzo[*cd*,*f*]azulene containing structural units of pyrimidine, pyrrole, and benzazepine.

EXPERIMENTAL

Melting points were determined in open capillaries using digital melting point IA9100 series apparatus (ThermoFischer Scientific) and are uncorrected. IR spectra were obtained on a Perkin–Elmer FT-IR spectrophotometer Spectrum BX II in nujol. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ using residual $CHCl_3$ signals (7.29 and 77.3 ppm for ^1H and ^{13}C NMR spectra, respectively) as internal standard. Column chromatography was performed using Silica gel 60 (0.040–0.063 mm) (Merck). All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light.

Arylboronic acids were purchased from Sigma–Aldrich and were used without further purification. Compound **1** was synthesized according to a procedure described in [32].

Methyl 5-amino-7-methyl-2-methylthio-4-phenyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (2a). A solution of compound **1** (0.1 g, 0.35 mmol) in anhydrous dioxane (25 ml) was flushed with argon and phenylboronic acid (46 mg, 0.38 mmol), K_3PO_4 (0.23 g, 1.08 mmol), 2.5 mol% $Pd(OAc)_2$ (1.9 mg, 0.009 mmol) and 5 mol% PPh_3 (4.7 mg,

0.018 mmol) were added under stirring and argon flow. The reaction mixture was refluxed under argon for 9 h. Then dioxane was evaporated to dryness. Water was

added to a residue and the obtained solution was extracted with chloroform. After evaporation of chloroform the solid was recrystallized to give 34 mg (30%) of compound **2a** as a yellow solid, mp 158°C (dec.) (2-propanol). IR spectrum, ν, cm^{-1}: 3380, 3367 (NH_2), 1670 (CO). ^1H NMR spectrum, δ, ppm: 2.69 (3H, s, SCH_3); 3.95(3H, s, NCH_3); 3.99 (3H, s, $COOCH_3$); 5.11 (2H, s, NH_2); 7.55–7.60 (3H, m, H Ph); 7.77–7.79 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.60; 30.99; 51.37; 103.69; 107.30; 129.05; 129.12; 130.45; 136.54; 137.80; 151.60; 162.13; 163.63; 169.11. Found, %: C 58.33; H 5.02; N 17.21. $C_{16}H_{16}N_4O_2S$. Calculated, %: C 58.52; H 4.91; N 17.06.

Methyl 5-amino-4-(4-*tert*-butylphenyl)-7-methyl-2-methylthio-7H-pyrrolo[2,3-*d*]py-rimidine-6-carboxylate (2b). A solution of compound **1** (0.15 g, 0.52 mmol) in anhydrous dioxane (5 ml) was flushed with argon and 4-*tert*-butylphenylboronic acid (121 mg, 0.68 mmol), 2 mol% $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), 4 mol% dicyclohexyl-(2-biphenyl)phosphine (7.4 mg, 0.021 mmol), and K_3PO_4 (0.29 g, 1.37 mmol) were added under stirring and argon flow. The reaction mixture was refluxed under argon for 5 h. Then dioxane was evaporated to dryness and water was added to a residue. The obtained solution was extracted with benzene, organic layer dried with Na_2SO_4, filtered and solvents were evaporated to dryness. The obtained solid was purified by column chromatography (eluent–benzene) to give 0.16 g (80%) of compound **2b** as yellow solid, mp 153–155°C. IR spectrum, ν, cm^{-1}: 3453, 3350 (NH_2), 1667 (CO). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (9H, s, *t*-Bu); 2.69 (3H, s, SCH_3); 3.96 (3H, s, NCH_3); 3.99 (3H, s, OCH_3); 5.29 (2H, br. s, NH_2); 7.60 (2H, d, *J* = 8.1, H Ph); 7.76 (2H, d, *J* = 8.1, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.6; 31.1; 31.5; 35.2; 51.4; 103.5; 107.3; 125.4; 126.2; 129.0; 136.8; 151.3; 154.2; 161.8; 163.6; 168.6. Found, %: C 62.66; H 6.39; N 14.51. $C_{20}H_{24}N_4O_2S$. Calculated, %: C 62.48; H 6.29; N 14.57.

Methyl 5-amino-4-(3,5-dichlorophenyl)-7-methyl-2-methylthio-7H-pyrrolo[2,3-*d*]-pyrimidine-6-carboxylate (2c). A solution of compound **1** (0.1 g, 0.35 mmol) in anhydrous dioxane (5 ml) was flushed with argon and 3,50-dichlorophenylboronic acid (87 mg, 0.46 mmol), 2 mol% $Pd(OAc)_2$ (1.6 mg, 0.007 mmol), 4 mol% dicyclohexyl-(2-biphenyl)phosphine (4.9 mg, 0.014 mmol), and K_3PO_4 (0.19 g, 0.9 mmol) were added. The reaction mixture was refluxed under argon for 3 h. Then dioxane was evaporated to dryness and water was added to a residue. The obtained solution was extracted with benzene, organic layer dried with Na_2SO_4, filtered and filtrate concentrated to 1/3 of the initial volume. The solution was filtered through the layer of silica gel, silica gel was once washed with benzene. After the evaporation of solvents the residue was recrystallized to give 89.1 mg (64%) of compound **2c** as a yellow solid, mp 202–204°C (2-propanol). IR spectrum, ν, cm^{-1}: 3377, 3269 (NH_2), 1679 (CO). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.69 (3H, s, SCH_3); 3.97 (3H, s, NCH_3); 4.00 (3H, s, OCH_3); 4.77 (2H, br. s, NH_2); 7.56–7.57 (1H, dd, *J* = 1.8, *J* = 2.1, H Ph); 7.70–7.71 (2H, dd, *J* = 1.8, *J* = 2.1, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.6; 31.1; 51.6; 103.5; 108.1; 127.7; 130.5; 135.6; 135.8; 140.3; 151.4; 158.8; 163.5; 169.0. Found, %: C 48.63; H 3.50; N 14.32. $C_{16}H_{14}Cl_2N_4O_2S$. Calculated, %: C 48.37; H 3.55; N 14.10.

Methyl 4-chloro-5-diacetylamino-7-methyl-2-methylthio-7H-pyrrolo[2,3-*d*]py-rimidine-6-carboxylate (3). A mixture of compound **1** (1.0 g, 3.5 mmol) and acetic anhydride (20 ml) was refluxed for 3.5 h. Acetic anhydride was removed under reduced pressure and the remaining solid recrystallized to give 0.82 g (63%) of compound **3**, mp 125.5–127°C (2-propanol). IR spectrum, ν, cm^{-1}: 1720, 1708 (CO). ^1H NMR spectrum, δ, ppm: 2.34 (6H, s, $2COCH_3$); 2.64 (3H, s, SCH_3); 3.91 (3H, s, NCH_3); 4.10 (3H, s, OCH_3). Found, %: C 45.73; H 4.05; N 15.15. $C_{14}H_{15}ClN_4O_4S$. Calculated, %: C 45.35; H 4.08; N 15.11.

Methyl 4-methyl-2-methylthio-4H-1,3,4,6-tetraazadibenzo[*cd*,*f*]azulene-5-carb-

oxylate (5) was synthesized from compound **1** and 2-formylphenylboronic acid according to the procedure described for compound **2c**. The reaction time 2 h. The yield 88%, mp 199–201°C. IR spectrum, ν, cm^{-1}: 1702 (CO). ^1H NMR spectrum, δ, ppm: 2.70 (3H, s, SCH_3); 4.06 (3H, s, NCH_3); 4.07 (3H, s, $COOCH_3$); 7.60–7.65 (3H, m, H Ph); 8.14 (1H, s, CH); 8.88–8.91 (1H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.7; 31.4; 52.7; 109.6; 120.7; 128.6; 129.0; 132.8; 133.1; 135.1; 136.0; 138.1; 151.7; 157.6; 160.0; 162.2; 169.8. Found, %: C 60.22; H 3.98; N 16.39. $C_{17}H_{14}N_4O_2S$. Calculated, %: C 60.34; H 4.17; N 16.56.

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