A New Strategy for the Triarylation of Pyrrolopyrimidines through Microwave-Promoted Cross-Coupling Reactions

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A new pyrrolo[2,3-*d*]pyrimidines bearing three aryl groups at 2-, 4- and 6-positions were prepared by arylation of 7-methyl-2-methylthio-4-chloro-6-phenylpyrrolo[2,3-*d*]pyrimidine (**6**) with the corresponding arylboronic acid under Suzuki-Miyaura conditions, followed by a second arylation using a Liebeskind-Srogl cross-coupling reaction. A parallel study beginning by the C-2 chemoselective arylation of **6** under Liebeskind-Srogl conditions followed by Suzuki-Miyaura coupling at C-4 was carried out and the results compared. All the tranformations have been realized under microwave irradiation.

Introduction

The pyrrolo[2,3-*d*]pyrimidines also known as deazapurines, due to their structural similarity to natural purines, constitute interesting templates for drug discovery programs in medicinal chemistry[1] and have proved valuable scaffolds in organic chemistry.[2] Compounds bearing a pyrrolopyrimidine nucleus have shown a variety of biological effects including antibacterial,[3] antiinflammatory,[4] antiparasitic[5] and antitumor.[6] In addition to these pharmaceutical applications, substituted arylpyrimidine, arylpurine or deazapurine cores with π-conjugated systems exhibit interesting photophysical properties.[7]

Diaryl-, triaryl- and tetraarylpurines have been prepared by intramolecular pyrimidine cyclizations[8] and/or using nucleophilic substitutions of halogenated purines.[9] The C-4 and C-2 consecutive diarylation of purines using Pd-catalysed classical Suzuki-Miyaura conditions was reported by Hocek et al.[9a-b] The same authors prepared selectively 4,5-diarylpyrrolo[2,3-*d*]pyrimidines from 4-(phenylsulfanyl)-5-iodopyrrolo[2,3-*d*]pyrimidine.[10] Tumkevicius et al. obtained 2,4,7-triarylpyrrolo[2,3-*d*]pyrimidines from the corresponding 2,4-dichloropyrrolopyrimidines by a combination of Suzuki-Miyaura cross-couplings with arylboronic acids and *N*-arylation reactions with aryl halides.[11]

In a previous work related to the synthesis of pyrrolopyrimidines, we began by stepwise arylation at the C-4 and C-5 positions of 6-aryl-4,6-dihalopyrrolo[2,3-*d*]pyrimidines[12] and more recently we reported a one-pot synthesis of 4,6-disubstituted pyrrolopyrimidines.[13] The substitution of pyrrolopyrimidines is often difficult to control and the selectivity plays an special role when different substituents need to be introduced.[14]

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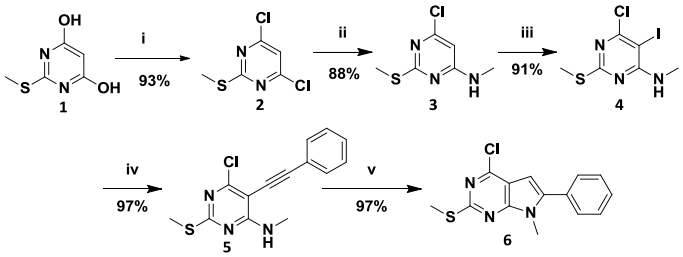
In the current work, a more selective strategy was developed to obtain 2,4,6-triaryl pyrrolo[2,3-*d*]pyrimidines from 4-chloro-6-phenyl-7-methyl-2-methylthiopyrrolo[3,2-*d*]pyrimidines. The presence of different leaving groups at C-2 and C-4 positions of the heterocycle allows a major selectivity for the arylation through Suzuki-Miyaura and Liebeskind-Srogl conditions.

Results and Discussion

Retrosynthetic analysis suggested that 2,4,6-trisubstituted pyrrolo[2,3-*d*]pyrimidines (IUPAC numbering is used throughout the manuscript) could be synthesized by a general approach from monocyclic compounds involving intramolecular cyclization and double arylation under cross-coupling conditions. Among several possibilities, we chose to prepare a versatile key intermediate for the formation of 2,4,6-triarylated pyrrolo-pyrimidines from the commercially available 4,6-dihydroxy-2-methylthiopyrimidine (**1**).

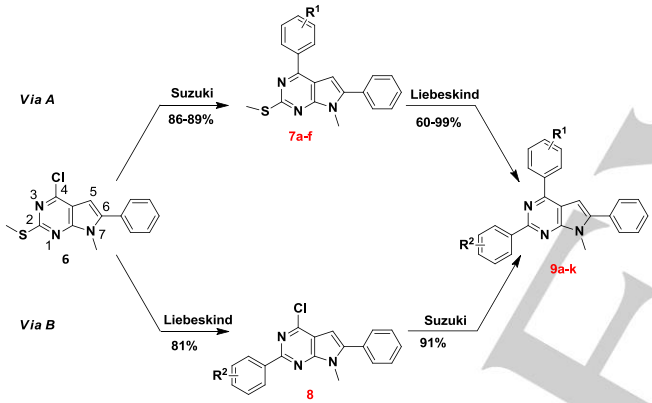
4,6-Dichloro-2-methylthiopyrimidine (**2**) was obtained with 93% yield by applying the procedure of Raboisson et al., which involved dichlorination of 4,6-dihydroxy-2-methylthiopyrimidine with $POCl_3$ and *N,N*-diethylaniline.[15] The 5-alkynylpyrimidine **5** was prepared by direct and regioselective substitution of **2** with methylamine, followed successively by iodination with NIS at the C-5 position of 4-chloro-6-methylamino-2-methylthiopyrimidine (**3**) and Sonogashira type alkynylation with phenylacetylene under microwave irradiation.



Scheme 1. i) $POCl_3$, *N,N*-diethylaniline, ii) $CH_3NH_2.HCl$, NEt_3, *i*PrOH, reflux, 8 h, iii) NIS, CH_3CN, MW, 100 °C, 15 min, iv) $Pd(dba)_2$, P(*o*-furyl)$_3$, CuI, phenylacetylene THF/NEt_3, MW, 100 °C, 30 min, v) Cs_2CO_3, CH_3CN, MW, 100 °C, 30 min.

The last step consists of the intramolecular cyclization of the acetylene derivative **5** to the 6-arylated deazapurine **6** under the conditions established previously by us for related compounds.[13]

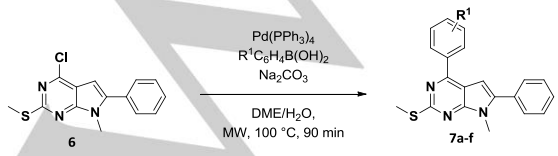
Our synthetic route toward the target **6** was based on a combination of five steps with an overall yield of 70% (Scheme 1). Considering the attraction of a concise and rapid synthetic procedure that would allow the preparation of a series of 2,4,6-trisubstituted pyrrolopyrimidines, among the different transformations envisioned, we were primarily interested in the arylation of the heterocyclic intermediate **6**. Thus, 7-methyl-2-methylthio-4-chloro-6-phenylpyrrolo[2,3-*d*]pyrimidine (**6**) was considered to be an important substructure, with application beyond the current work. Retrosynthetic analysis suggested two general approaches for the preparation of 2,4,6-trisubstituted pyrrolopyrimidines from the key building block **6** (*Via A* and *B*, Scheme 2).

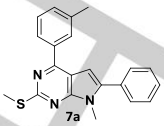
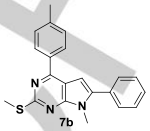
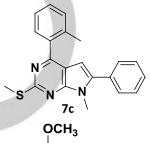
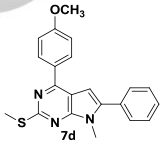
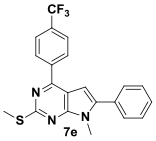
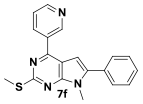


Scheme 2. Approaches towards the of pyrrolopyrimidine derivatives

A Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 4-halopyrrolopyrimidines with arylboronic acids could be followed by $Pd(PPh_3)_4$/CuTC-catalyzed C-2 arylation with arylboronic acid under Liebeskind-Srogl conditions (*Via A*), or the sequence could be performed in reverse (*Via B*). Both arylation reactions were catalyzed by palladium to generate C-C bonds. A set of six substituted phenylboronic acids has been chosen as the reagents for the arylation at the C-2 and C-4 positions (Tables 1 and 3).

Table 1. Arylation under Suzuki-Miyaura reaction conditions



Entry	R^1	Compound	Yield[a]
1	3-CH_3		86%
2	4-CH_3		92%
3	2-CH_3		98%
4	4-CH_3O		99%
5	4-CF_3		94%
6	3-pyridyl		98%

[a] Yield of isolated and purified compound

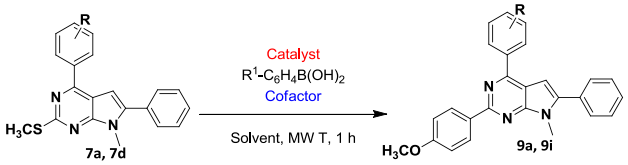
To explore this double arylation process and highlight its synthetic interest the new compounds **7a-f** were prepared by arylation at the C-4 position of pyrrolopyrimidine **6** with different arylboronic acids under Suzuki-Miyaura conditions and microwave irradiation. According to the results, it seems that neither the position of the substituent (Table 1, entries 1-3) nor its nature (electron-donating, entries 1-4 or electron-withdrawing, entry 5) affected the behaviour of this reaction (Table 1, entries 1-6). In addition, the pyridine heterocyclic system also provided an excellent yield (Table 1, entry 6).

Following route A, the next step was the desulfuration at the C-2 position under Liebeskind-Srogl conditions.[16] Optimization of the Liebeskind-Srogl cross-coupling reaction was carried out on the diarylated intermediates **7a** and **7d** using the corresponding arylboronic acid and modifying the catalyst and the thiophilic metal co-catalyst (Table 2). The solvent and temperature were also modified (Table 2, entry 4). The desulfurative coupling in nitrogenated aromatic thioethers (**7a** and **7d**) with boronic acids proceeded with higher yields when using copper (I) 3-methylsalicylate (CuMeSal) (Table 2, entries 1 and 5) rather than copper (I) thiophene-2-carboxylate (CuTC) (Table 2, entries 2-4 and 6). In an aromatic nucleus, the replacement of the methylthio group generally gives the corresponding compounds in low yields.[17] In this case the presence of electronegative

nitrogen in the aromatic nucleus (at the alpha position of the heterocycle) favours the cross-coupling reaction.[18]

This arylation was performed under microwave irradiation in THF at 100 °C for 1 h using $Pd(PPh_3)_4$ as the catalyst and CuMeSal as a co-catalyst. CuTC was less effective than CuMeSal and led to an unfinished reaction, which was confirmed by the observation of a mixture of the triarylated derivative (**9**) and the starting material (**7**) (Table 2, entries 3, 4, and 6).

Table 2. Optimization of the Liebeskind-Srogl cross-coupling reaction



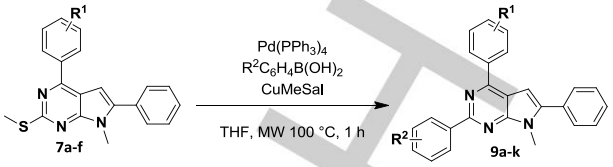
Entry	R	Catalyst	Cofactor	Solvent	T (°C)	Yield %(**9**)	Yield % (**7**)
1	3-CH_3 (**7a**)	$Pd(PPh_3)_4$	CuMeSal	THF	100	93[b] (**9a**)	-
2	3-CH_3 (**7a**)	$Pd(PPh_3)_4$	CuTC	THF	100	93 (**9a**)	-
3	4-CH_3O (**7d**)	$Pd(PPh_3)_4$	CuTC	THF	100	64[a] (**9i**)	36[a] (**7d**)
4	4-CH_3 O (**7d**)	$Pd(PPh_3)_4$	CuTC	Dioxane	130	68[a] (**9i**)	32[a] (**7d**)
5	4-CH_3O (**7d**)	$Pd(PPh_3)_4$	CuMeSal	THF	100	88[b] (**9i**)	-
6	4-CH_3O (**7d**)	$Pd_2(dba)_3$, P(*o*-furyl)$_3$	CuTC	THF	100	49[a] (**9i**)	51[a] (**7d**)

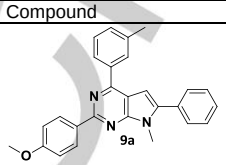
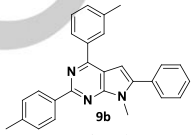
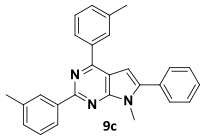
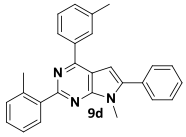
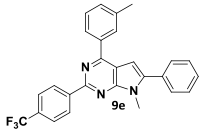
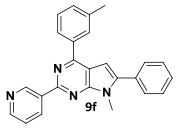
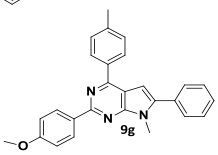
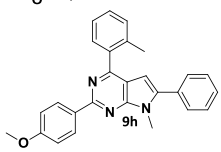
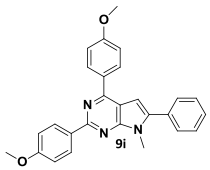
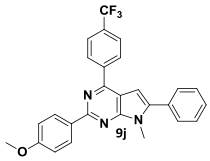
[a] Ratio determined by ^{1}H-NMR. [b] Yield of isolated and purified compound

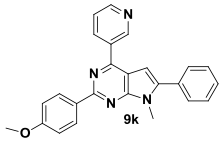
The optimized Liebeskind-Srogl conditions were applied to methylthio deazapurines (**7a**-**f**) to explore the scope of this reaction.

According to the results obtained, the electronic character of the substituents of the arylboronic acids does not seem to be important (electron-donating substituents, Table 3, entries 1-4 and 7-11 and electron-withdrawing, entry 5). Nitrogenated heterocycles such as pyridine also led to good yields (Table 3, entry 6). Nevertheless, the position of the substituent influenced the reaction process, as evidenced by *ortho*-methylphenyl group of the compound **9d** (Table 3, entry 4). In this case, the yield was lower due to hindrance.

Table 3. Arylation under Liebeskind-Srogl reaction conditions

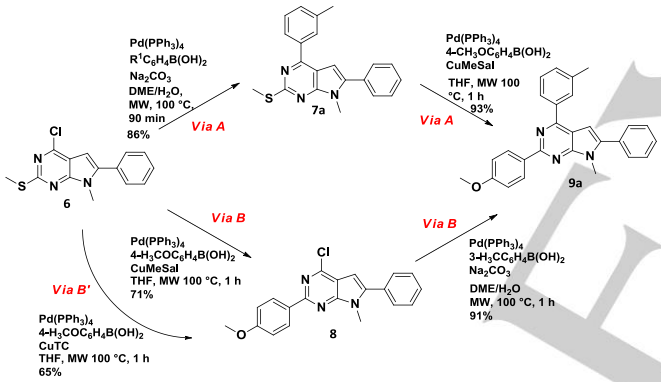


Entry	R^1	R^2	Compound	Yield[a]
1	3-CH_3	4-CH_3O		93%
2	-	4-CH_3		99%
3	-	3-CH_3		89%
4	-	2-CH_3		60%
5	-	4-CF_3		95%
6	-	3-pyridyl		96%
7	4-CH_3	4-CH_3O		97%
8	2-CH_3	-		95%
9	4-CH_3O	-		88%
10	4-CF_3	-		99%
11	3-pyridyl	-		86%



[a] Yield of isolated and purified compound

Finally, the diarylation process was carried out reversing the order of then two steps (*Via B*). Thus, arylation of **6** under Liebeskind-Srogl conditions at 100 °C (external temperature) regioselectively afforded the deazapurine **8,** which was obtained by displacement of the methylthio group located between two nitrogen atoms of compound **6** (Scheme 3). Subsequent arylation at position 4 under previously optimized Suzuki conditions led to the triaryl pyrrolopyrimidine **9a** (Scheme 3). Bearing in mind not only the lower yield obtained by *Via B* (65%) compared with that of the *Via A (80%)*, but also the difficulty in isolating the product, this route was discarded. As in *Via A*, in the *route B* both co-factors of the Liebeskind reaction were tested in *Via B*, a better result being obtained with CuMeSal (*Via B*) than with CuTC (*Via B'*) (overall yield of 65% versus 59%).



Scheme 3. Comparison of both routes (*A* and *B*) for the arylation at C-2 and C-4 positions of pyrrolopyrimidines

In this work related to Suzuki-Miyaura and Liebeskind-Srogl couplings as well as in others previously realized,[12-13] we have used microwave irradiation. The use of microwave irradiation compared to the conventional heating method increases the yield significantly and accelerates the reaction rate. In general, the use of microwave irradiation provides a change of thermodynamic properties of the reagents. This is revealed by the reduction of Gibbs free energy of activation of chemical reaction caused by the storage of microwave energy as energy of vibration of the reagent or substrate structure known as enthalpy effect. [19]

Conclusions

An efficient and robust route to prepare 2,4,6-triarylated pyrrolo[2,3-*d*]pyrimidines has been developed from the key intermediate **6**. Of the two alternative routes explored, the more efficient was Suzuki-Miyaura cross-coupling followed by a Liebeskind reaction, which provided higher yields and a broader substrate scopes than the process in reverse. The process which starts with the arylation at C-2 using Liebeskind-Srogl conditions turns out to be less effective. The use of microwave irradiation accelerates the reaction rate providing the arylated pyrrolopyrimidines in excellent yields.

A variety of substituents can be selectively introduced at the C-2 and C-4 positions of the nucleus of pyrrolopyrimidine **6**. It is notable that substituents can be introduced at the C-2 and C-4 positions during the last steps of the synthesis, thereby providing an efficient approach to the construction of a compound library. Also this aproach will be used for the preparation of compounds related to pyrrolopyrimidines.

Experimental Section

General information: Microwave-assisted reactions were carried out in a Biotage Initiator Microwave synthesis instrument and the external temperature was measured by an IR sensor. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254, Merck) plates. Compounds were visualized by UV irradiation. Column chromatography was performed with silica gel 60 (230-400 mesh, 0.040-0.063 mm). Melting points (Mp) were obtained on a MFB-595010M Gallenkamp apparatus with a digital thermometer in open capillary tubes and are reported without correction. IR spectra were obtained using FTIR Perkin-Elmer 1600 Infrared Spectrophotometer.^{1}H, and ^{13}C NMR spectra were recorded on a Bruker 250 MHz (^{13}C, 63 MHz), Varian Gemini-300 (75.5 MHz), Varian Gemini-400 (100 MHz) and Bruker 400 MHz (100 MHz).^{19}F NMR spectra were recorded on a Bruker (376 MHz, $CDCl_3$) using C_6F_6 as an internal standard (δ 0 ppm). Chemical shifts are reported in parts per million (ppm) relative to the central peak of the solvent: $CDCl_3$ (δ, 7.26 (H) and 77.16 (C)), CD_3OD (δ, 3.31 (H) and 49.45 (C)), DMSO-d_6 (δ, 2.49 (H) and 39.51 (C)) as internal standards. The following abbreviations are used for the proton spectra multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Maxis Bruker 4G by the ICOA platform of the University of Orléans (France) or on a LC/MSD-TOF (2006) (Agilent technologies) by the «Center of mass spectrometry» of the University of Barcelona (Spain). All reagents were of high quality or purified before use. Organic solvents were of analytical grade or were purified by standard procedures.

General Procedure A (Amination): To a solution of dichloropyrimidine (1.0 mmol) in isopropanol (1.0 mL), triethylamine (1.2 mmol) and amine (1.2 mmol) were added. The reaction was stirred at the reflux of isopropanol (or of amine if is inferior) until complete consumption of the starting material as determined by TLC analysis. After cooling, the solvent was removed under vacuo. Water (15 mL) was added and then the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with NH_4Cl (10 mL). The evaporation of the

solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

General Procedure B (Pyrimidine iodination): A solution of *N*-methylpyrimidin-4-amine (1.0 mmol) and NIS (3.0 mmol) in acetonitrile (2 mL) was transferred to a special microwave tube and irradiated in a microwave oven at 100 °C for 15 minutes. The progress of the reaction was monitored by TLC analysis. After cooling, the solvent was removed. Dichloromethane (20 mL) was added and the organic layer was washed with $Na_2S_2O_3$ (aqueous saturated solution, 2 x 16 mL), and NaOH (10%, 2 x 16 mL). The evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography or recrystallization.

General Procedure C (Sonogashira coupling): A mixture containing the compound 5-iodopyrimidine (1.0 mmol), alkyne (2.0 mmol), $Pd(dba)_2$ (0.03 mmol), tri(2-furyl)phosphine (0.06 mmol) and CuI (0.04 mmol) in dry THF (1 mL) and dry triethylamine (3.5 mL) was transferred to a special microwave tube and irradiated in a microwave oven at 100 °C for 30 minutes. The progress of the reaction was monitored by TLC. After cooling, the mixture was diluted with NH_4Cl (aqueous saturated solution, 15 mL) and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and filtered through Celite®. The evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

General Procedure D (Cyclization): A solution of the alkyne (1.0 mmol) and cesium carbonate (1.0 mmol) in acetonitrile (4.5 mL) was transferred to a special microwave tube and irradiated in a microwave oven at 100 °C for the required time. The progress of the reaction was monitored by TLC. After cooling, the solvent was removed under vacuo. Water (20 mL) was added to the mixture and the crude of reaction was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with Na_2CO_3 (aqueous saturated solution, 15 mL) and brine (15 mL). The evaporation of the solvent under reduced pressure gave the crude product which was directly purified by silica gel column chromatography.

General Procedure E (Suzuki-Miyaura coupling at C-4): Under gas pressure of argon, a mixture of 4-chloropyrrolo[2,3-*d*]pyrimidine (1.0 mmol), boronic acid (1.05 mmol), sodium carbonate (2.0 mmol) and *tetrakis*(triphenylphosphine)palladium (0.02 mmol) in a degassed solvent mixture of DME (3.8 mL) and H_2O (0.6 mL) was transferred to a special microwave tube and irradiated in a microwave oven at 100 °C for 60-90 minutes. The progress of the reaction was monitored by TLC. After cooling, the mixture was diluted with a mixture of brine and water (1:1) (20 mL) and the aqueous solution was extracted with ethyl acetate (3 x 20 mL). The evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

General Procedure F (Liebeskind-Srogl coupling at C-2): Under gas pressure of argon, a mixture of 2-(methylthio)-4,6-diarylpyrrolo[2,3-*d*]pyrimidine (1.0 mmol), boronic acid (1.5 mmol), CuMeSal (3.0 mmol) and *tetrakis*(triphenylphosphine)palladium (0.1 mmol) in degassed THF (8.0 mL) and was transferred to a special microwave tube and irradiated in a microwave oven at 100 °C for 60 minutes. The progress of the reaction was monitored by TLC. After cooling, the mixture was diluted with dichloromethane (20 mL) and washed with a saturated solution of Na_2CO_3 until total discoloration of the aqueous solution extracted. The evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

4,6-Dichloro-2-(methylthio)pyrimidine (2): 2-Methylsulfanyl-pyrimidin-4,6-diol (2.00 g, 12.6 mmol) and *N*,*N*-diethylaniline (3.65 mL) were added slowly to phosphorus oxychloride (23.3 mL) while cooling on ice. The mixture was slowly warmed till reflux and refluxed for 2.5 hours. The mixture was then evaporated, added to crushed ice and extracted three times with ethyl acetate and the combined organic layers were washed three times with water, once with brine and concentrated. The crude product was purified by silica gel column chromatography petroleum ether/dichloro methane 9:1) affording **2** as colourless crystals in 93% of yield (2.30 g, 11.8 mmol); mp 42-43 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2956, 2928, 2855, 1539, 1532, 1509, 1469, 1358, 1272, 1215, 1099, 843, 825, 809; ^{1}H RMN (400 MHz, $CDCl_3$) δ, 2.57 (s, 3H, SCH_3), 6.89 (s, 1H, H_5); ^{13}C RMN (100 MHz, $CDCl_3$) δ, 13.9 (CH_3), 115.6 (CH), 161.2(2Cql), 174.1(Cq); HRMS (ESI): calcd for $C_5H_5Cl_2N_2S$ $[M+H]^+$: 194.9545, found 194.9539.

6-Chloro-*N*-methyl-2-(methylthio)pyrimidin-4-amine (3): The reaction was carried out following the general procedure A starting from 4,6-dichloro-2-(methylthio)pyrimidine **2** (2.30 g, 11.8 mmol) and $MeNH_2$.HCl (955 mg, 14.1 mmol). The reaction was stirred at the reflux of isopropanol. The crude product was purified by silica gel column chromatography dichloromethane/ethyl acetate 6:4) affording **3** as off-white solid in 88% of yield (1.97 g, 10.4 mmol); mp 129-131 °C (ethyl acetate); IR (ATR diamond, cm-1) v: 3261, 3138, 2928, 1564, 1493, 1423, 1360, 1273, 1224, 1117, 965, 806, 677; ^{1}H RMN (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, SCH_3), 2.93 (s, 3H, NCH_3), 5.40 (s, 1H, NH), 6.03 (s, 1H, H_5); ^{13}C RMN (100 MHz, $CDCl_3$) δ: 14.2 (CH_3), 28.4 (CH_3), 96.4 (CH), 159.4 (Cq), 163.6 (Cq), 172.1 (Cq); HRMS (ESI): calcd for $C_6H_9ClN_3S$ $[M+H]^+$: 190.0200 , found 190.0197.

6-Chloro-5-iodo-*N*-methyl-2-(methylthio)pyrimidin-4-amine (4): The reaction was carried out following the general procedure B starting from the pyrimidine **3** (1.90 g, 10.0 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 5:5) affording **4** as white solid in 91% of yield (2.89 g, 9.17 mmol); mp 142-144 °C (ethyl acetate); IR (ATR diamond, cm-1) v: 3397, 3378, 2919, 1564, 1526, 1483, 1410, 1375, 1321, 1254, 1221, 1135, 1096, 992, 931, 825, 750; ^{1}H RMN (400 MHz, $CDCl_3$) δ: 2.51 (s, 3H, SCH_3), 3.05 (s, *J* = 4.9 Hz, 3H, NCH_3), 5.55 (s, 1H, NH); ^{13}C RMN (100 MHz, $CDCl_3$) δ: 14.5 (CH_3), 29.4 (CH_3), 72.9 (Cq), 161.6 (Cq), 162.0 (Cq), 171.7 (Cq); HRMS (ESI): calcd for $C_6H_8ClIN_3S$ $[M+H]^+$: 315.9167, found 315.9162.

6-Chloro-*N*-methyl-2-(methylthio)-5-(phenylethynyl)pyrimidin-4-amine (5): The reaction was carried out following the general procedure C starting from the iodinated pyrimidine **4** (2.22 g, 7.04 mmol) and

phenylacetylene (1.54 mL, 14.1 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 6:4) affording **5** as yellow solid in 95% of yield (1.93 mg, 6.67 mmol); mp 131-133 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3342, 2932, 1553, 1488, 1366, 1220, 1082, 938, 853, 811, 751, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H, SCH_3), 3.11 (d, *J* = 5.0 Hz, 3H, NCH_3), 5.67 (s, 1H, NH), 7.34-7.41 (m, 3H, H-Ar), 7.50-7.57 (m, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4 (CH_3), 28.4 (CH_3), 80.2 (Cq), 96.1 (Cq), 101.4 (Cq), 122.4 (Cq), 128.6 (2CH), 129.1 (CH), 131.6 (2CH), 158.7 (Cq), 162.1 (Cq), 170.8 (Cq); HRMS (ESI): calcd for $C_{14}H_{13}ClN_3S$ $[M+H]^+$: 290.0513, found 290.0510.

4-Chloro-7-methyl-2-(methylthio)-6-phenyl-7*H*-pyrrolo[2,3-*d*] pyrimidine (6): The reaction was carried out following the general procedure D starting from the alkyne **5** (1.87 g, 6.45 mmol) and microwave irradiation was applied for 30 minutes. The crude p roductwas purified by silica gel column chromatography (petroleum ether/dichloromethane 5:5) affording **6** as off-white solid in 97% of yield (1.81 mg, 6.25 mmol); mp 94-96 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2930, 1587, 1531, 1486, 1375, 1236, 1179, 1127, 960, 866, 748, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.66 (s, 3H, SCH_3), 3.79 (s, 3H, NCH_3), 6.53 (s, 1H, H_5), 7.46-7.54 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (SCH_3), 30.4 (NCH_3), 98.9 (CH), 114.2 (Cq), 129.0 (2CH), 129.1 (CH), 129.2 (2CH), 131.1 (Cq), 141.8 (Cq), 150.6 (Cq), 151.4 (Cq), 152.7 (Cq); HRMS (ESI): calcd for $C_{14}H_{13}ClN_3S$ $[M+H]^+$: 290.0513, found 290.0511.

7-Methyl-2-(methylthio)-6-phenyl-4-(m-tolyl)-7*H*-pyrrolo[2,3-d]pyrimidine (7a): The reaction was carried out following the general procedure E starting from the 4-chloropyrrolopyrimidine **6** (300 mg, 1.04 mmol) and 3-tolylboronic acid (147.8 mg, 1.09 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 7:3) affording **7a** as yellow solid in 86% of yield (308 mg, 0.890 mmol); mp 152-155 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2924, 1557, 1485, 1358, 1333, 1261, 1147, 962, 744, 700M; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H, CH_3), 2.74 (s, 3H, SCH_3), 3.84 (s, 3H, NCH_3), 6.78 (s, 1H, H_5), 7.31 (d, *J* = 7.5 Hz, 1H, H-Ar), 7.41 (t, *J* = 7.7 Hz, 1H, H-Ar), 7.44-7.59 (m, 5H, H-Ar), 7.96 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.99 (s, 1H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7 (CH_3), 21.7 (CH_3), 30.1 (CH_3), 100.2 (CH), 112.8 (Cq), 126.2 (CH), 128.6 (CH), 128.8 (CH), 128.9 (2CH), 129.2 (2CH), 129.6 (CH), 130.9 (CH), 131.8 (Cq), 138.2 (Cq), 138.5 (Cq), 141.5 (Cq), 154.7 (Cq), 157.1 (Cq), 164.0 (Cq); HRMS (ESI): calcd for $C_{21}H_{20}N_3S$ $[M+H]^+$: 346.1372, found 346.1370.

7-Methyl-2-(methylthio)-6-phenyl-4-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*] pyrimidine (7b): The reaction was carried out following the general procedure E starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and 4-tolylboronic acid (24.6 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 5:5) affording **7b** as pale yellow solid in 92% of yield (55.0 mg, 0.159 mmol); mp 106-108 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2924, 1553, 1487, 1362, 1334, 1262, 1179, 1147, 954, 835, 750, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H, CH_3), 2.74 (s, 3H, SCH_3), 3.83 (s, 3H, NCH_3), 6.78 (s, 1H, H_5), 7.33 (d, *J* = 7.9 Hz, 2H, H-Ar), 7.42-7.52 (m, 3H, H-Ar), 7.53-7.58 (m, 2H, H-Ar), 8.10 (d, *J* = 7.9 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (CH_3), 21.6 (CH_3), 30.1 (CH_3), 100.1 (CH), 112.6 (Cq), 128.7 (CH), 128.8 (2CH), 128.9 (2CH), 129.1 (2CH), 129.5 (2CH), 131.7 (Cq), 135.5 (Cq), 140.3 (Cq), 141.4 (Cq), 154.7 (Cq), 156.7 (Cq), 163.9 (Cq); HRMS (ESI): calcd for $C_{21}H_{20}N_3S$ $[M+H]^+$: 346.1372 found 346.1371.

7-Methyl-2-(methylthio)-6-phenyl-4-(*o*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (7c): The reaction was carried out following the general procedure E starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and 2-tolylboronic acid (24.6 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 2:8) affording **7c** as dark yellow solid in 98% of yield (58.6 mg, 0.170 mmol); mp 74-76 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2922, 2359, 1557, 1489, 1357, 1332, 1254, 1184, 1142, 958, 750, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H, CH_3), 2.70 (s, 3H, SCH_3), 3.85 (s, 3H, NCH_3), 6.39 (s, 1H, H_5), 7.28-7.37 (m, 3H, H-Ar), 7.42-7.55 (m, 6H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ, 14.6 (CH_3), 20.5 (CH_3), 30.1 (CH_3), 100.1 (CH), 114.6 (Cq), 125.7 (CH), 128.8 (CH), 128.9 (2CH), 129.1 (2CH), 129.2 (CH), 130.0 (CH), 131.2 (CH), 131.7 (Cq), 136.9 (Cq), 137.3 (Cq), 141.4 (Cq), 154.2 (Cq), 159.5 (Cq), 163.8 (Cq); HRMS (ESI): calcd for $C_{21}H_{20}N_3S$ $[M+H]^+$: 346.1372 found 346.1372.

4-(4-Methoxyphenyl)-7-methyl-2-(methylthio)-6-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (7d): The reaction was carried out following the general procedure E starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and 4-methoxyphenylboronic acid (27.5 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 2:8) affording **7d** as yellow solid in 99% of yield (62.0 mg, 0.172 mmol); mp 55-57 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2924, 1553, 1509, 1488, 1336, 1250, 1171, 1029, 956, 838, 748, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.73 (s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, NCH_3), 6.77 (s, 1H, H_5), 7.04 (d, *J* = 8.3 Hz, 2H, H-Ar), 7.42-7.58 (m, 5H, H-Ar), 8.18 (d, *J* = 8.3 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (CH_3), 30.1 (CH_3), 55.5 (CH_3), 100.1 (CH), 112.2 (Cq), 114.1 (2CH), 128.7 (CH), 128.8 (2CH), 129.1 (2CH), 130.5 (2CH), 130.8 (Cq), 131.7 (Cq), 141.2 (Cq), 154.7 (Cq), 156.3 (Cq), 161.3 (Cq), 163.8 (Cq); HRMS (ESI): calcd for $C_{21}H_{20}N_3OS$ $[M+H]^+$: 362.1322, found 362.1319.

7-Methyl-2-(methylthio)-6-phenyl-4-(4-(trifluoromethyl)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (7e): The reaction was carried out following the general procedure E starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and (4-(trifluoromethyl)phenyl)boronic acid (34.4 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 6:4) affording **7e** as light green solid in 94% of yield (64.7 mg, 0.162 mmol); mp 131-133 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2923, 1557, 1489, 1358, 1331, 1254, 1184, 1142, 958, 758, 750, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.73 (s, 3H, SCH_3), 3.84 (s, 3H, NCH_3), 6.74 (s, 1H, H_5), 7.46-7.58 (m, 5H, H-Ar), 7.77 (d, *J* = 8.1 Hz, 2H, H-Ar), 8.27 (d, *J* = 8.1 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (CH_3), 30.1 (CH_3), 99.5 (CH), 113.0 (Cq), 124.2 (q, *J* = 272 Hz, Cq), 125.7 (q, *J* = 4 Hz, 2CH), 128.9 (2CH), 129.0 (CH), 129.1 (2CH), 129.3 (2CH), 131.4 (Cq), 131.5 (Cq), 131.7 (q, *J* = 32 Hz, Cq), 141.6 (Cq), 142.4 (Cq), 154.9 (Cq), 164.1 (Cq); ^{19}F NMR (376

MHz, $CDCl_3$) δ: -62.66 (CF_3); HRMS (ESI): calcd for $C_{21}H_{17}F_3N_3S$ $[M+H]^+$: 400.1090 found 400.1088.

7-Methyl-2-(methylthio)-6-phenyl-4-(pyridin-3-yl)-7*H*-pyrrol[2,3-*d*]pyrimidine (7f): The reaction was carried out following the general procedure E starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and 3-pyridinylboronic acid (22.3 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate 6:4) affording **7f** as yellow solid in 98% of yield (54.5 mg, 0.169 mmol); mp 137-139 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2997, 1542, 1487, 1359, 1323, 1268, 1193, 1154, 1024, 956, 744, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.73 (s, 3H, SCH_3), 3.85 (s, 3H, NCH_3), 6.77 (s, 1H, H_5), 7.44-7.57 (m, 6H, H-Ar), 8.48 (d, *J* = 7.8 Hz, 1H, H-Ar), 8.72 (s, 1H, H-Ar), 9.41 (s, 1H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7 (CH_3), 30.2 (CH_3), 99.4 (CH), 112.9 (Cq), 123.4 (CH), 129.0 (2CH), 129.1 (CH), 129.2 (2CH), 131.4 (Cq), 134.1 (Cq), 136.2 (CH), 142.4 (Cq), 150.1 (CH), 150.9 (CH), 153.8 (Cq), 154.8 (Cq), 164.3 (Cq); HRMS (ESI): calcd for $C_{19}H_{17}N_4S$ $[M+H]^+$: 333.1168 found 333.1167.

4-Chloro-2-(4-methoxyphenyl)-7-methyl-6-phenyl-7*H*-pyrrolo [2,3-*d*]pyrimidine (8): The reaction was carried out following the general procedure F starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and 4-methoxyphenylboronic acid (39.3 mg, 0.259 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 2:8) affording **8** as beige solid in 81% of yield (48.9 mg, 0.140 mmol); mp 125-126 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2925, 1588, 1530, 1463, 1394, 1244, 1168, 1129, 1022, 954, 761, 743; ^{1}H NMR (400 MHz, CDCl3) δ: 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, NCH_3), 6.59 (s, 1H, H_5), 7.00 (d, *J* = 8.4 Hz, 2H, H-Ar), 7.45-7.58 (m, 5H, H-Ar), 8.50 (d, *J* = 8.4 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.4 (NCH_3), 55.5 (OCH_3), 98.9 (CH), 113.9 (2CH), 115.5 (Cq), 129.0 (2CH), 129.1 (CH), 129.2 (2CH), 129.8 (2CH), 130.5 (Cq), 131.3 (Cq), 142.9 (Cq), 151.5 (Cq), 153.8 (Cq), 157.6 (Cq), 161.5 (Cq); HRMS (ESI): calcd for $C_{20}H_{17}ClN_3O$ $[M+H]^+$: 350.1055, found 350.1052.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(*m*-tolyl)-7*H*-pyrrolo [2,3-*d*]pyrimidine (9a): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7a** (50 mg, 0.15 mmol) and 4-methoxyphenylboronic acid (33.0 mg, 0.22 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 5:5) affording **9a** as pale yellow solid in 93% of yield (54.7 mg, 0.14 mmol). mp 138-140 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3053, 2915, 1550, 1512, 1487, 1374, 1299, 1243, 1166, 1031, 748, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.51 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, NCH_3), 6.86 (s, 1H, H_5), 7.05 (d, *J* = 8.2 Hz, 2H, H-Ar), 7.33 (d, *J* = 7.0 Hz, 1H, H-Ar), 7.44-7.61 (m, 6H, H-Ar), 8.16-8.04 (m, 2H, H-Ar), 8.67 (d, *J* = 8.2 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8 (CH_3), 30.1 (CH_3), 55.5 (CH_3), 100.2 (CH), 113.8 (2CH), 114.0 (Cq), 126.3 (CH), 128.6 (CH), 128.8 (CH), 128.9 (2CH), 129.2 (2CH), 129.7 (2CH), 129.8 (CH), 130.7 (CH), 132.0 (Cq), 132.2 (Cq), 138.5 (Cq), 139.1 (Cq), 142.6 (Cq), 154.8 (Cq), 156.7 (Cq), 157.6 (Cq), 161.1 (Cq); HRMS (ESI): calcd for $C_{27}H_{24}N_3O$ $[M+H]^+$: 406.1914, found 406.1910.

7-Methyl-6-phenyl-4-(*m*-tolyl)-2-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9b): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and 4-tolylboronic acid (29.5 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 7:3) affording **9b** as yellow solid in 99% of yield (56.1 mg, 0.144 mmol); mp 153-154 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3052, 2916, 2855, 1552, 1488, 1374, 1304, 1262, 1168, 834, 766, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.96 (s, 3H, NCH_3), 6.88 (s, 1H, H_5), 7.35 (d, *J* = 7.6 Hz, 3H, H-Ar), 7.45-7.55 (m, 4H, H-Ar), 7.58-7.63 (m, 2H, H-Ar), 8.09-8.18 (m, 2H, H-Ar), 8.64 (d, *J* = 7.8 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6 (CH_3), 21.8 (CH_3), 30.0 (CH_3), 100.2 (CH), 114.2 (Cq), 126.3 (CH), 128.1 (2CH), 128.6 (CH), 128.8 (CH), 128.9 (2CH), 129,1 (2CH), 129.2 (2CH), 129.6 (CH), 130.7 (CH), 131.9 (Cq), 136.7 (Cq), 138.4 (Cq), 139.0 (Cq), 139.5 (Cq), 142.8 (Cq), 154.7 (Cq), 156.6 (Cq), 157.7 (Cq); HRMS (ESI): calcd for $C_{27}H_{24}N_3$ $[M+H]^+$: 390.1965 found 390.1963.

7-Methyl-6-phenyl-2,4-di-*m*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (9c): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and 3-tolylboronic acid (29.5 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 7:3) affording **9c** as pale yellow solid in 89% of yield (50.3 mg, 0.129 mmol); mp 154-156 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3047, 2917, 1552, 1488, 1394, 1373, 1261, 920, 861, 768, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 6H, $2CH_3$), 3.98 (s, 3H, NCH_3), 6.88 (s, 1H, H_5), 7.28 (d, *J* = 7.7 Hz, 1H, H-Ar), 7.34 (d, *J* = 7.6 Hz, 1H, H-Ar), 7.40-7.55 (m, 5H, H-Ar), 7.58-7.63 (m, 2H, H-Ar), 8.06-8.16 (m, 2H, H-Ar), 8.49-8.56 (m, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8 ($2CH_3$), 30.1 (CH_3), 100.2 (CH), 114.4 (Cq), 125.4 (CH), 126.3 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH)128.9 (2CH), 129.2 (2CH), 129.7 (CH), 130.4 (CH), 130.8 (CH), 131.9 (Cq), 138.0 (Cq), 138.5 (Cq), 139.0 (Cq), 139.3 (Cq), 143.0 (Cq), 154.7 (Cq), 156.8 (Cq), 157.8 (Cq); HRMS (ESI): calcd for $C_{27}H_{24}N_3$ $[M+H]^+$: 390.1964 found 390.1966.

7-Methyl-6-phenyl-4-(*m*-tolyl)-2-(*o*-tolyl)-7*H*-pyrrolo[2,3-*d*] pyrimidine (9d): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and 2-tolylboronic acid (29.5 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 7:3) affording **9d** as white solid in 60% of yield (34.0 mg, $8.73.10^{-2}$ mmol), mp 114-116 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3056, 2918, 1549, 1488, 1396, 1375, 1260, 745, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.94 (s, 3H, NCH_3), 6.91 (s, 1H, H_5), 7.30-7.38 (m, 4H, H-Ar), 7.42-7.56 (m, 4H, H-Ar), 7.59-7.65 (m, 2H, H-Ar), 8.02-8.12 (m, 3H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8 ($2CH_3$), 30.2 (CH_3), 100.0 (CH), 113.7 (Cq), 126.0 (CH), 126.3 (CH), 128.7 (CH), 128.9 (2CH), 129.3 (3CH), 129.7 (2CH), 130.7 (CH), 130.9 (CH), 131.3 (CH), 131.9 (Cq), 137.4 (Cq), 138.5 (Cq), 138.9 (Cq), 139.8 (Cq), 143.0 (Cq), 154.4 (Cq), 156.6 (Cq), 160.3 (Cq); HRMS (ESI): calcd for $C_{27}H_{24}N_3$ $[M+H]^+$: 390.1965 found 390.1963.

7-Methyl-6-phenyl-4-(*m*-tolyl)-2-(4-(trifluoromethyl)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9e): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and (4-(trifluoromethyl)phenyl)boronic acid (41.2 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 7:3) affording **9e** as white solid in 95% of yield (61.1 mg, 0.138 mmol); mp 137-139 °C (pentane). IR (ATR diamond, cm^{-1}) v: 2917, 1551, 1318, 1165, 1119, 1063, 858, 769, 747, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (s, 3H, CH_3), 3.95 (s, 3H, NCH_3), 6.89 (s, 1H, H_5), 7.32-7.39 (m, 1H, H-Ar), 7.45-7.62 (m, 6H, H-Ar), 7.77 (d, *J* = 8.0 Hz, 2H, H-Ar), 8.06-8.15 (m, 2H, H-Ar), 8.83 (d, *J* = 7.9 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8 (CH_3), 30.1 (CH_3), 100.3 (CH), 114.9 (Cq), 124.6 (q, *J* = 272 Hz, Cq), 125.4 (q, *J* = 4 Hz, 2CH), 126.3 (CH), 128.4 (2CH), 128.7 (CH), 129.0 (3CH), 129.2 (2CH), 129.6 (CH), 130.9 (CH), 131.1 (q, *J* = 32 Hz, Cq), 131.7 (Cq), 138.6 (Cq), 138.7 (Cq), 142.7 (Cq), 143.6 (Cq), 154.5 (Cq), 156.0 (Cq), 156.7 (Cq); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.39 (CF_3); HRMS (ESI): calcd for $C_{27}H_{21}F_3N_3$ $[M+H]^+$: 444.1682 found 444.1680.

7-Methyl-6-phenyl-2-(pyridin-3-yl)-4-(*m*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9f). The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and 3-pyridinylboronic acid (26.7 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate 85:15) affording **9f** as pale yellow solid in 96% of yield (52.3 mg, 0.139 mmol); mp 136-138 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3053, 2918, 1538, 1487, 1373, 1290, 909, 777, 749, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (s, 3H, CH_3), 3.93 (s, 3H, NCH_3), 6.87 (s, 1H, H_5), 7.32-7.36 (m, 1H, H-Ar), 7.42-7.55 (m, 5H, H-Ar), 7.56–7.60 (m, 2H, H-Ar), 8.04-8.14 (m, 2H, H-Ar), 8.95 (d, *J* = 6.6 Hz, 1H, H-Ar). We lose two signals of pyridine's hydrogen; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8 (CH_3), 30.1 (CH_3), 100.3 (CH), 114.8 (Cq), 126.2 (CH), 128.7 (CH), 128.9 (2CH), 129.0 (CH), 129.2 (2CH), 129.6 (CH), 130.0 (CH), 130.9 (CH), 131.6 (Cq), 132.1 (Cq), 132.2 (Cq), 135.1 (CH), 138.5 (Cq), 138.7 (Cq), 143.5 (Cq), 149.7 (CH), 154.4 (Cq), 155.6 (CH), 156.7 (Cq); HRMS (ESI): calcd for $C_{25}H_{21}N_4$ $[M+H]^+$: 377.1761 found 377.1760.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9g): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7b** (50 mg, 0.145 mmol) and 4-methoxyphenylboronic acid (33.0 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 5:5) affording **9g** as yellow solid in 97% of yield (56.9 mg, 0.140 mmol); mp 169-171 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3048, 2917, 1552, 1509, 1464, 1375, 1299, 1244, 1161, 1035, 840, 749, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, NCH_3), 6.86 (s, 1H, H_5), 7.05 (d, *J* = 8.5 Hz, 2H, H-Ar), 7.38 (d, *J* = 7.7 Hz, 2H, H-Ar), 7.42-7.54 (m, 3H, H-Ar), 7.59 (d, *J* = 7.2 Hz, 2H, H-Ar), 8.24 (d, *J* = 7.8 Hz, 2H, H-Ar), 8.68 (d, *J* = 8.5 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6 (CH_3), 30.1 (CH_3), 55.5 (CH_3), 100.2 (CH), 113.7 (Cq), 113.8 (2CH), 128.7 (CH), 128.8 (2CH), 129.0 (2CH), 129.1 (2CH), 129.5 (2CH), 129.6 (2CH), 132.0 (Cq), 132.2 (Cq), 136.3 (Cq), 140.0 (Cq), 142.5 (Cq), 154.8 (Cq), 156.4 (Cq), 157.5 (Cq), 161.1 (Cq); HRMS (ESI): calcd for $C_{27}H_{24}N_3O$ $[M+H]^+$: 406.1914 found 406.1910.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(*o*-tolyl)-7*H*-pyrrolo [2,3-*d*]pyrimidine (9h): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7c** (50 mg, 0.145 mmol) and 4-methoxyphenylboronic acid (33.0 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 2:8) affording **9h** as white solid in 95% of yield (55.8 mg, 0.138 mmol); mp 128-130 °C (pentane); IR (ATR diamond, cm^{-1}) v: 3057, 2929, 1560, 1376, 1300, 1246, 1160, 1031, 842, 759, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 3.97 (s, 3H, NCH_3), 6.51 (s, 1H, H_5), 7.03 (d, *J* = 8.6 Hz, 2H, H-Ar), 7.32-7.37 (m, 1H, H-Ar), 7.37-7.42 (m, 2H, H-Ar), 7.43-7.52 (m, 3H, H-Ar, H-Ar), 7.56 (d, *J* = 7.3 Hz, 2H, H-Ar), 7.67 (d, *J* = 7.3 Hz, 1H, H-Ar), 8.62 (d, *J* = 8.6 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.7 (CH_3), 30.0 (CH_3), 55.5 (CH_3), 100.1 (CH), 113.8 (2CH), 115.7 (Cq), 125.7 (CH), 128.7 (CH), 128.8 (2CH), 129.0 (CH), 129.1 (2CH), 129.7 (2CH), 130.1 (CH), 131.3 (CH), 131.9 (Cq), 132.2 (Cq), 137.1 (Cq), 138.0 (Cq), 142.4 (Cq), 154.3 (Cq), 157.3 (Cq), 159.1 (Cq), 161.1 (Cq); HRMS (ESI): calcd for $C_{27}H_{24}N_3O$ $[M+H]^+$: 406.1914 found 406.1913.

2,4-*Bis*(4-Methoxyphenyl)-7-methyl-6-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (9i). The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7d** (50.0 mg, 0.138 mmol) and 4-methoxyphenylboronic acid (31.5 mg, 0.207 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 2:8) affording **9i** as yellow solid in 88% of yield (51.2 mg, 0.121 mmol); mp 155-156 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2918, 1605, 1510, 1459, 1372, 1248, 1158, 1026, 837, 750, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.91 (s, 6H, OCH_3), 3.94 (s, 3H, NCH_3), 6.85 (s, 1H, H_5), 7.04 (d, *J* = 7.9 Hz, 2H, H-Ar), 7.09 (d, *J* = 7.9 Hz, 2H, H-Ar), 7.44-7.55 (m, 3H, H-Ar), 7.56-7.63 (m, 2H, H-Ar), 8.31 (d, *J* = 7.9 Hz, 2H, H-Ar), 8.66 (d, *J* = 7.9 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.1 (CH_3), 55.5 (CH_3), 55.6 (CH_3), 100.2 (CH), 113.3 (Cq), 113.8 (2CH), 114.2 (2CH), 128.7 (CH), 128.9 (2CH), 129.2 (2CH), 129.6 (2CH), 130.5 (2CH), 131.8 (Cq), 132.0 (Cq), 132.2 (Cq), 142.4 (Cq), 154.8 (Cq), 156.0 (Cq), 157.4 (Cq), 161.1 (Cq), 161.2 (Cq); HRMS (ESI): calcd for $C_{27}H_{24}N_3O_2$ $[M+H]^+$: 422.1863, found 422.1864.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(4-(trifluoromethyl) phenyl)-7H-pyrrolo[2,3-*d*]pyrimidine (9j): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7e** (50 mg, 0.125 mmol) and 4-methoxyphenylboronic acid (28.5 mg, 0.188 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane 7:3) affording **9j** as light green solid in 99% of yield (57.1 mg, 0.124 mmol); mp 150-152 °C (pentane); IR (ATR diamond, cm^{-1}) v: 2936, 1565, 1378, 1320, 1247, 1166, 1107, 1030, 843, 755, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.91 (s, 3H, OCH_3), 3.95 (m, 3H, NCH_3), 6.81 (s, 1H, H_5), 7.05 (d, *J* = 8.5 Hz, 2H, H-Ar), 7.45-7.56 (m, 3H, H-Ar), 7.56-7.63 (m, 2H, H-Ar), 7.82 (d, *J* = 8.0 Hz, 2H, H-Ar), 8.40 (d, *J* = 8.0 Hz, 2H, H-Ar), 8.65 (d, *J* = 8.5 Hz, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.1 (CH_3), 55.5 (CH_3), 99.6 (CH), 113.9 (2CH), 114.1 (Cq),

124.6 (q, *J* = 271 Hz, Cq), 125.7 (q, *J* = 4 Hz, 2CH), 129.0 (2CH), 129,1 (CH), 129.2 (2CH), 129.3 (2CH), 129.7 (2CH), 131.5 (q, *J* = 32 Hz, Cq), 131.7 (Cq), 131.8 (Cq), 142.5 (Cq), 143.5 (Cq), 154.6 (Cq), 155.0 (Cq), 157.6 (Cq), 161.3 (Cq); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.61 (CF_3); HRMS (ESI): calcd for $C_{27}H_{21}F_3N_3O$ $[M+H]^+$: 460.1631 found 460.1629.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(pyridin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9k): The reaction was carried out following the general procedure F starting from the 4-arylpyrrolopyrimidine **7f** (50 mg, 0.155 mmol) and 4-methoxyphenylboronic acid (28.5 mg, 0.233 mmol). The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate 6:4) affording **9k** as yellow solid in 86% of yield (52.6 mg, 0.134 mmol); mp 166-167 °C (pentane); IR (ATR diamond, cm^{-1}) ν: 3048, 2926, 1583, 1557, 1488, 1374, 1302, 1239, 1163, 1024, 853, 752, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, NCH_3), 6.83 (s, 1H, H_5), 7.03 (d, *J* = 8.3 Hz, 2H, H-Ar), 7.44-7.55 (m, 4H, H-Ar), 7.58 (d, *J* = 7.4 Hz, 2H, H-Ar), 8.62 (m, 3H, H-Ar), 8.84 (s, 1H, H-Ar), 9.58 (s, 1H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.1 (CH_3), 55.5 (CH_3), 99.4 (CH), 113.9 (2CH), 114.0 (Cq), 124.1 (CH), 128.8 (Cq), 128.9 (2CH), 129.0 (CH), 129.1 (2CH), 129.6 (2CH), 131.6 (Cq), 131.7 (Cq), 136.1 (CH), 143.4 (Cq), 150.0 (CH), 150.5 (CH), 153.4 (Cq), 154.8 (Cq), 157.6 (Cq), 161.2 (Cq); HRMS (ESI): calcd for $C_{25}H_{21}N_4O$ $[M+H]^+$: 393.1710 found 393.1709.

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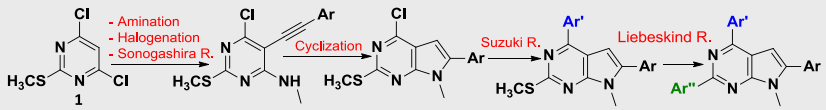
A New Strategy for the Triarylation of Pyrrolopyrimidines through Microwave-Promoted Cross-Coupling Reactions



Several triarylpyrrolopyrimidines were readily prepared from the 4,6-dichloro-2-methylthiopyrimidine in excellent yields by effective cross coupling reactions. An advantage of this method is the tolerance of various substituted aryl groups.

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C- Arylation

Vanessa Prieur, M. Dolors Pujol* and Gérald Guillaumet***……1-10**

A New Strategy for the Triarylation of Pyrrolopyrimidines through Microwave-Promoted Cross-Coupling Reactions

Keywords: pyrrolopyrimidines • Suzuki-Miyaura • Liebeskind-Srogl • microwave irradiation • arylation