Palladium-Catalysed Coupling of 4-Halopyrrolo[2,3-*d*]pyrimidines with Arylacetylenes: Synthesis of a New Heterocyclic System – 4*H*-Pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole

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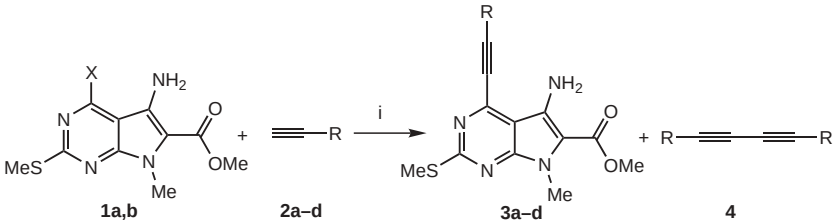
Abstract: Palladium-catalysed reaction of methyl 5-amino-4-chloro(or iodo)-7-methyl-2-methylthiopyrrolo[2,3-*d*]pyrimidine-6-carboxylate with arylacetylenes affords the corresponding 4-(arylethynyl)pyrrolopyrimidines. Reaction of 5-amino-4-iodopyrrolopyrimidine with 2-ethynyl-*N*-mesylaniline in the presence of $PdCl_2(PPh_3)_2$ and CuI led to the formation of 5-amino-4-(1-mesylindol-2-yl)pyrrolopyrimidine which after the removing of mesyl group cyclised with ethyl orthoformate to give the first representative of a novel heterocycle – 4*H*-pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole.

Key words: palladium, catalysis, arylacetylenes, pyrrolopyrimidines, cyclisation, pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole

Alkynes are versatile intermediates in synthesis[1] as well as an important functional moiety in a wide range of biologically active compounds.[2] The development of methods for alkynyl group introduction into organic molecules is an important target. For this purpose the Sonogashira reaction has enjoyed tremendous success because of the mild reaction conditions and great tolerance of nearly all types of functional groups.[3] As the pyrrolo[2,3-*d*]pyrimidine heterosystem represents a 7-deazaanalogue of biogenic purine it is an important class of compounds possessing notable biological activities.[4] Nevertheless the Sonogashira reaction in the pyrrolo[2,3-*d*]pyrimidine series has not been studied extensively yet. To the best of our knowledge, there are only few examples of functionalisation of a pyrrole moiety of pyrrolo[2,3-*d*]pyrimidine via the Sonogashira reaction[5] and no work has been done with pyrrolo[2,3-*d*]pyrimidines bearing halogeno groups in a pyrimidine moiety. In this context and as continuation of our ongoing program aimed at the synthesis of the pyrimidine moiety containing heterosystems[6] we report herein the synthesis of 4-(arylethynyl)pyrrolo[2,3-*d*]pyrimidines and implementation of the obtained results for the synthesis of a novel heterocycle – pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole. The work was also stimulated by reports that 6-alkenyl and 6-(2-arylethyl)purines are highly active as cytokinins.[7]

An easily available methyl 5-amino-4-chloro-7-methyl-2-methylthiopyrrolo[2,3-*d*]pyrimidine-6-carboxylate[6b] (**1a**) reacted with arylacetylenes **2a**–**c** at 60–70 °C in the presence 10 mol% $PdCl_2(PPh_3)_2$ and 20 mol% CuI to form the corresponding 4-(arylethynyl)pyrrolopyrimidines **3a**–**c** in 56–60% yields (Scheme 1).

Although the coupling reactions were carried out under argon, the Sonogashira reaction between **1a** and arylacetylenes was always accompanied by the formation of some amount of diacetylenes **4**. Formation of by-products **4** was



2, 3	R	Yield
a	C_6H_5	60%
b	4-Me-C_6H_4	60%
c	4-F-C_6H_4	56%
d	2-NH_2-C_6H_4	62%

Scheme 1 *Reagents*: i) $PdCl_2(PPh_3)_2$, PPh_3, CuI, Et_3N, DMF; ii) 67% HI, Me_2CO, r.t., 8 h.

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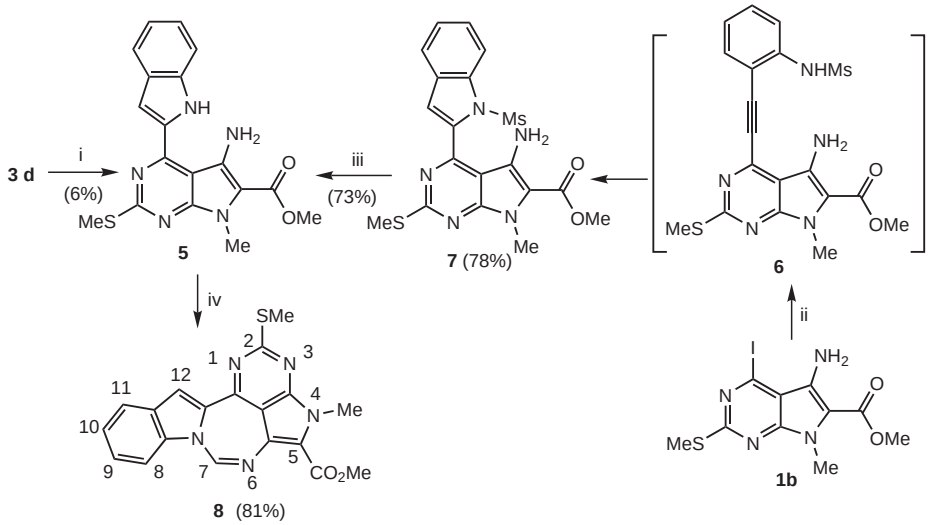
found to depend on the nature of substituent in benzene ring and solvent. For example, in the reaction of **1a** with 4-fluorophenylacetylene (**2c**) performed in DMF using 2 equivalents of Et_3N only traces of diacetylene were observed, whereas in the reaction of **1a** with 4-methylphenylacetylene (**2b**) under the same reaction conditions the target compound **3b** and the corresponding diacetylene **4** were isolated in 60% and 15% yield, respectively.[8] Moreover, the corresponding diacetylene **4** (R = 4-MeC_6H_4) was obtained as the main reaction product when the reaction was carried out only in Et_3N. To synthesise the desired 4-(arylethynyl)pyrrolopyrimidines **3a**–**c** from **1a** in reasonable yields an excess (10 equiv) of acetylenes **2a**–**c** had to be used. However, synthesis of compound **3d** was achieved only from 4-iodo derivative **1b**, which was obtained in 91% yield by the reaction of **1a** with 67% hydroiodic acid in acetone.[9] The best results for the synthesis **3d** were obtained when the reaction was carried out in Et_3N and 1.4 equivalents of 2-ethynylaniline (**2d**), 2 mol% of $PdCl_2(PPh_3)_2$ and 20 mol% CuI were used.[10]

Among the most efficient procedures for indole system synthesis are methods starting from 2-ethynylaniline derivatives, which can be heteroannulated to deliver indoles by many types of reagents, among the most frequently used being palladium complexes[11] and, more recently, copper salts.[12] However, heating **3d** with CuI in DMF at 100 °C led to a complex reaction mixture from which 4-(2-indolyl)pyrrolo[2,3-*d*]pyrimidine (**5**) was isolated only in 6% yield (Scheme 2). On the other hand, electron-withdrawing groups such as mesyl, acetyl, trifluoroacetyl or ethoxycarbonyl groups attached to the amino group of 2-ethynylanilines can facilitate their cyclisation into the appropriate indoles.[13] Therefore, 4-iodopyrrolopyrimidine (**1b**) was allowed to react with 2-ethynyl-*N*-mesylaniline in the presence of $PdCl_2(PPh_3)_2$ and CuI at room temperature. It was noticed that along with the cross-coupling reaction of **1b** with 2-ethynyl-*N*-mesylaniline cyclisation of the formed 4-(2-mesylaminophenylethynyl) derivative **6** occurred to give 4-(1-mesyl-2-indolyl)pyrrolopyrimidine (**7**). This prompted us to develop a one-pot synthesis of **7** from 4-iodopyrrolopyrimidine (**1b**): when coupling reaction at room temperature between **1b** and 2-ethynyl-*N*-mesylaniline had completed additional amount of CuI was added and the reaction temperature was raised to 50–60 °C. 4-(1-Mesyl-2-indolyl)pyrrolopyrimidine (**7**) was isolated in 78% yield.[14] *N*-Mesyl derivative **7** was deprotected to give 4-(2-indolyl)pyrrolopyrimidine (**5**) by heating with KOH in methanol.[15]

Heating **5** with an excess of ethyl orthoformate at 100–110 °C in the presence of ammonium chloride furnished methyl 4-methyl-2-methylthio-4*H*-pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole-5-carboxylate (**8**) – the first representative of a novel heterocyclic system.[16] In the ^1H NMR spectrum of compound **8** a signal for C7-H appeared at δ = 8.48 ppm, while characteristic signals of the NH and NH_2 groups, which in the ^1H NMR spectrum of compound **5** are correspondingly observed at δ = 9.6 ppm and 5.59 ppm, disappears from the ^1H NMR spectrum. IR spectrum of **8** also does not contain absorption bands for the amino groups. The ^{13}C NMR and elemental analysis data are consistent with the structure of **8**.

In summary, we have developed a simple and efficient synthesis of a novel pentacyclic heterosystem – pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole, containing structural units of indole, pyrrolo[2,3-*d*]pyrimidine and 1,3-diazepine. Work is now in progress to establish the scope and limitations of this novel route to the synthetic target **8** as well as application of 4-(arylethynyl)pyrrolopyrimidines for the preparation of 4-alkenyl- and 4-(2-arylethyl)pyrrolopyrimidines as structural analogues of the naturally occurring and synthetic purines with cytokinin properties.



Scheme 2 *Reagents*: i) CuI, DMF, 100 °C, 12 h; ii) 1. 2-ethynyl-N-mesylaniline, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, r.t., 3 h, 2. CuI, 50–60 °C, 3 h; iii) KOH, MeOH, reflux, 45 min; iv) $HC(OEt)_3$, NH_4Cl, 100–110 °C, 8 h.

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(8) **Typical Procedure for the Synthesis of Methyl 5-Amino-4-(arylethynyl)-2-methylthiopyrrolo[2,3-*d*]pyrimidine-6-carboxylates (3a–c).**[17]
Through a mixture of compound **1a**[6b] (0.20 g, 0.70 mmol), CuI (26 mg, 0.14 mmol), PPh_3 (0.10 g, 0.38 mmol), $PdCl_2(PPh_3)_2$ (49 mg, 0.07 mmol), Et_3N (0.2 mL, 0.14 g, 1.4 mmol) and DMF (3.0 mL) was bubbled Ar for 10 min. Then 4-methylphenylacetylene (**2b**) (0.80 g, 6.95 mmol) was added dropwise at 60–70 °C (bath temperature). The reaction mixture was stirred at 60–70 °C for 1 h and then cooled to –5 °C. The precipitate was filtered off, washed with cold 2-PrOH and purified by chromatography on silica gel eluting with $CHCl_3$ to give 0.12 g (15%, calculated in respect of **2b**) of di(4-methylphenyl)-1,3-butandiyne (**4b**), mp 180–181 °C (from 1-BuOH), R_f = 0.5 ($CHCl_3$), lit.[18] mp 183 °C, and 0.15 g (60%) of compound **3b**, mp 157.0–158.5 °C (from MeCN), R_f = 0.4 ($CHCl_3$).

(9) **Methyl 5-Amino-4-iodo-2-methylthiopyrrolo[2,3-*d*]pyrimidine-6-carboxylate (1b)**.[17]
To a mixture, prepared by slow addition of 67% HI (15 mL) to acetone (15 mL), compound **1a (**1.5 g, 5.23 mmol) was added. The mixture was stirred for 8 h at r.t., then poured onto ice (24 g) and 20% NaOH solution (33 mL) was added. The reaction mixture was stirred for 2–5 h till the colour of precipitate turned into bright yellow. The solid was filtered, dried and recrystallised to give 1.8 g (91%) of compound **1b**, mp 160.5–161.0 °C (from 2-PrOH).

(10) **Methyl 5-Amino-4-(2-aminophenylethynyl)-2-methylthiopyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3d)**.[17]
Through a mixture of compound **1b** (0.40 g, 1.060 mmol), CuI (40 mg, 0.210 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol) and Et_3N (15 mL) was bubbled Ar for 10 min. The mixture was heated to 50 °C (bath temperature) and then a solution of acetylene **2d** (0.17 g, 1.450 mmol) in Et_3N (5 mL) was added dropwise. The reaction mixture was stirred under Ar at 55–60 °C for 1 h. The precipitate was filtered off and recrystallised to give 0.24 g (62%) of compound **3d**, mp 227–230 °C (from $CHCl_3$).

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(14) **Methyl 5-Amino-4-(1-mesylindol-2-yl)-2-methylthiopyrrolo[2,3-*d*]pyrimidine-6-carboxylate (7)**.
A mixture of compound **1b** (0.24 g, 0.63 mmol), CuI (0.06 g, 0.32 mmol), Et_3N (25 mL), DMF (2.5 mL), $PdCl_2(PPh_3)_2$ (0.045 g, 0.064 mmol) and 2-ethynyl-*N*-mesylaniline[13a] (0.15 g, 0.77 mmol) was stirred under Ar at r.t. for 3 h. Then CuI (0.18 g, 0.95 mmol) was added and the reaction mixture was stirred for additional 3 h at 50–60 °C (bath temperature). The reaction mixture was diluted with H_2O and extracted with Et_2O (3 × 70 mL). The combined organic extracts were dried over Na_2SO_4, evaporated and purified using dry column vacuum chromatography[19] (eluent: $CHCl_3$). The solid was recrystallised to give 0.22 g (78%) of compound **7**, mp 197.5–199.0 °C (from 2-PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, SCH_3), 3.71 (s, 3 H, SO_2CH_3), 3.96 (s, 3 H, NCH_3), 4.00 (s, 3 H, OCH_3), 5.25 (s, 2 H, NH_2), 7.06 (d, *J* = 0.5 Hz, 1 H, C3′-H), 7.41–7.35 (m, 1 H, C5′-H), 7.49 (ddd, *J* = 1.3 Hz, $J_{6'-5'}$ = 7.3 Hz, $J_{6'-7'}$ = 8.5 Hz, 1 H, C6′-H), 7.70 (d, $J_{4'-5'}$ = 7.7 Hz, 1 H, C4′-H), 8.13 (dd, *J* = 0.6 Hz, $J_{7'-6'}$ = 8.4 Hz, 1 H, C7′-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.4, 31.0, 43.7, 51.5, 104.5, 107.9, 113.9, 114.9, 122.3, 124.2, 126.5, 128.7, 135.1, 136.0, 137.9, 151.4, 153.3, 163.5, 168.1. IR (nujol): 3460, 3361 (NH_2), 1677 (CO) cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_5O_4S_2$: C, 51.22; H, 4.30; N, 15.72. Found: C, 51.55; H, 4.36; N, 15,76.

(15) **Methyl 5-Amino-4-(indol-2-yl)-2-methylthiopyrrolo[2,3-*d*]pyrimidine-6-carboxylate (5)**.[17]
A solution of compound **3** (50 mg, 0.11 mmol) in 5% KOH solution in MeOH (25 mL) was refluxed for 45 min, then cooled to r.t., poured into H_2O and extracted with Et_2O. Extract was dried over Na_2SO_4 and evaporated. The solid was recrystallised to give 30 mg (73%) of compound **5**, mp 172–174°C (from 2-PrOH).

(16) **Methyl 4-Methyl-2-methylthio-4*H*-pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole-5-carboxylate (8)**.
A mixture of compound **5** (30 mg, 0.08 mmol) and ethyl orthoformate (10 mL) was heated at 100–110 °C (bath temperature) for 2 h and NH_4Cl (5 mg, 0.09 mmol) was added. The reaction mixture was heated for additional 6 h and then cooled to r.t. The precipitate was filtered off, washed with cold EtOH and recrystallised to give 26 mg

(84%) of compound **8**, mp 267.0–268.5 °C (from DMF). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (s, 3 H, SCH_3), 4.10 (s, 3 H, NCH_3), 4.11 (s, 3 H, OCH_3), 7.39 (ddd, *J* = 0.9 Hz, $J_{10\text{-}9}$ = 7.3 Hz, $J_{10\text{-}11}$ = 8.0 Hz, 1 H, C10-H), 7.51 (ddd, *J* = 1.3 Hz, $J_{9\text{-}10}$ = 7.2 Hz, $J_{9\text{-}8}$ = 8.5 Hz, 1 H, C9-H), 7.73 (d, $J_{8\text{-}9}$ = 8.3 Hz, 1 H, C8-H), 7.78 (d, $J_{11\text{-}10}$ = 8.0 Hz, 1 H, C11-H), 8.01 (s, 1 H, C12-H), 8.48 (s, 1 H, C7-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.7, 31.4, 52.7, 106.3, 110.8, 113.6, 120.9, 123.2, 124.5, 127.1, 127.9, 128.6, 135.8, 137.1, 140.1, 150.1, 151.0, 162.2, 169.7. IR (nujol): 1694 (CO) cm^{-1}. Anal. Calcd for $C_{19}H_{15}N_5O_2S$: C, 60.47; H, 4.01; N, 18.56. Found: C, 60.85; H, 3.95; N, 18.24.

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