# Synthesis of 4-Alkynylpyrrolo[2,3-*d*]pyrimidines by Palladium-Catalyzed Cross-Coupling Reactions

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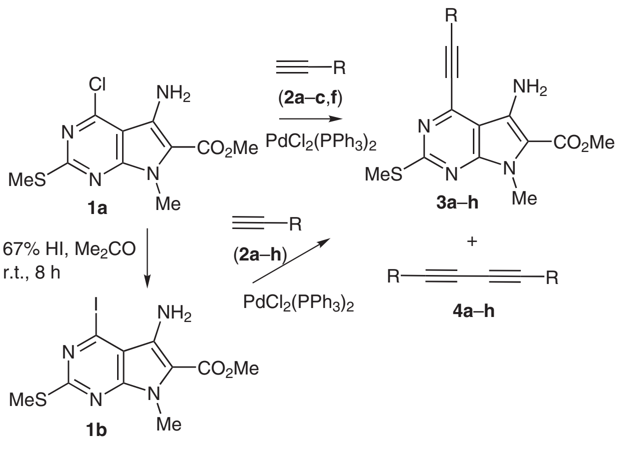
**Abstract:** The palladium-catalyzed cross-coupling reaction of methyl 5-amino-4-chloro- and 5-amino-4-iodo-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate with various terminal alkynes has been investigated. The 4-iodo derivative was found to be a good substrate for the synthesis of various 4-alkynylpyrrolopyrimidines. A simple synthesis of 4-(indol-2-yl)pyrrolo[2,3-*d*]pyrimidines by the reaction of 4-iodopyrrolopyrimidine with 2-ethynyl-*N*-mesylaniline in the presence dichlorobis(triphenylphosphine)palladium and copper(I) iodide is described.

**Key words:** palladium, alkyne, catalysis, heterocycle, pyrrolopyrimidine, cyclization

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 the introduction of the alkynyl group into organic molecules is an important target. For this purpose the Sonogashira reaction[3] has enjoyed tremendous success because of its mild reaction conditions and great tolerance to nearly all types of functional groups.[4] As the pyrrolo[2,3-*d*]pyrimidine heterosystem represents a 7-deaza analogue of biogenic purine, it is an important class of compounds possessing notable biological activity.[5,6a–e] Nevertheless the Sonogashira reaction in the pyrrolo[2,3-*d*]pyrimidine series has not, as yet, been extensively studied.[7] To the best of our knowledge, there are only few examples of the functionalization of the pyrrole moiety of pyrrolo[2,3-*d*]pyrimidine by the Sonogashira reaction[6] and no work has been done with pyrrolo[2,3-*d*]pyrimidines bearing halo groups in the pyrimidine moiety. Recently in our preliminary report,[8] we have shown that under the Sonogashira reaction conditions 5-amino-4-halo-2-(methylsulfanyl)pyrrolo[2,3-*d*]pyrimidine-6-carboxylates and arylacetylenes easily furnish the corresponding cross-coupling products. In the present paper we report a more extensive study on this palladium-catalyzed reaction with various terminal alkynes.

For the synthesis, methyl 5-amino-4-chloro-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1a**) was chosen as the starting material. The choice of **1a** was made for several reasons: (1) **1a** is easily obtained by a two-step procedure from 2,4-dichloro-2-(methylsulfanyl)pyrimidine-5-carbonitrile;[9] and (2) **1a** contains reactive groups, such as the methylsulfanyl, amino, and ester groups, that are useful for the functionalization of the molecule or performing cyclization reactions to give more complex heterocycles.

Thus, an investigation of the Sonogashira reaction of **1a** was expected to provide information on the tolerance of the cross-coupling reaction towards groups presented in the molecule and the possibility of using this reaction for the synthesis of various 4-alkynylpyrrolo[2,3-*d*]pyrimidines (Scheme 1).




**Scheme 1**

4-Chloropyrrolopyrimidine **1a** reacted with arylacetylenes **2a–c** at room temperature in *N*,*N*-dimethylformamide in the presence of 10 mol% dichlorobis(triphenylphosphine)palladium and 20 mol% copper(I) iodide using two equivalents of triethylamine to form the corresponding 4-(arylethynyl)pyrrolopyrimidines **3a–c** in 58–70% yields (method A, Table 1, entries 1–3); the reaction time was 16–28 hours. However the reaction of **1a** with hex-1-yne (**2f**) or propynol (**2h**) under these conditions did not give the desired compounds (Table 1, entries 4, 5); full conversion of **1a** in the reaction with **2f** or **2h** was not achieved even after 48 hours. Performing the reaction at 60–70 °C and using 0.54 equivalents of triphenylphosphine reduced the conversion time to 1–2 hours (method B). Although these conditions did not significantly affect the yield of 4-(arylethynyl)pyrrolo[2,3-*d*]pyrimidines **3a–c** (compare entries 1–3 with 6–9) this procedure allowed 4-hex-1-ynylpyrrolopyrimidine **3f** to be obtained in 65% yield (entry 9). However, reaction of

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**1a** with **2h** to give the corresponding 4-alkynylpyrrolopyrimidine **3h** failed (entry 10).

It should be mentioned that in order to achieve 100% conversion of **1a** and to synthesize the desired 4-alkynylpyrrolopyrimidines **3a–c**,**f** from **1a** in reasonable yields according to methods A and B an excess (10 equiv) of alkynes **2a–c**,**f** was used.

Moreover, the Sonogashira reaction between **1a** and alkynes was always accompanied by the formation of an amount of the diacetylenes **4**. Formation of byproducts **4** was found to depend on the nature of alkyne and solvent. For example, the reaction of **1a** with (4-fluorophenyl)acetylene (**2c**) in *N*,*N*-dimethylformamide using two equivalents of triethylamine gave only traces of diacetylene **4c**, whereas the reaction of **1a** with (4-methylphenyl)acetylene (**2b**) under the same conditions gave the target compound **3b** and the corresponding diacetylene **4b** in 60% and 15% yield, respectively (entry 7). Moreover, the corresponding diacetylene **4b** appeared to be the main reaction product, and no product of cross-coupling reaction was detected, when the reaction was carried out in triethylamine (entry 11).

Since the reaction of 4-chloropyrrolopyrimidine **1a** with some alkynes did not give satisfactory results, 4-iodo derivative **1b**, expected to be a more active substrate in the Sonogashira reaction, was synthesized. Compound **1b**

**Table 1** Optimization of the Sonogashira Reaction of 4-Chloro- and 4-Iodopyrrolo[2,3-*d*]pyrimidines **1a**,**b** with Alkynes **2a–h** To Give 4-Alkynylpyrrolo[2,3-*d*]pyrimidines **3a–h**

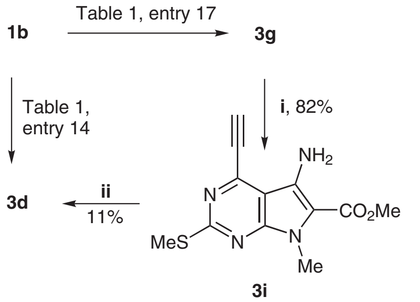
| Entry | Substrates | R | Method | CuI (mol%) | $PdCl_2(PPh_3)_2$ (mol%) | Alkyne (equiv) | Base, solvent | Temp (°C) | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a + 2a** | Ph | A | 20 | 10 | 10 | $Et_3N$ (2 equiv), DMF | r.t. | 18 | **3a** | 65 |
| 2 | **1a + 2b** | 4-$MeC_6H_4$ | A | 20 | 10 | 10 | $Et_3N$ (2 equiv), DMF | r.t. | 16 | **3b** | 70 |
| 3 | **1a + 2c** | 4-$FC_6H_4$ | A | 20 | 10 | 10 | $Et_3N$ (2 equiv), DMF | r.t. | 28 | **3c** | 58 |
| 4 | **1a + 2f** | Bu | A | 20 | 10 | 10 | $Et_3N$ (2 equiv), DMF | r.t. | 48 | – | – |
| 5 | **1a + 2h** | $CH_2OH$ | A | 20 | 10 | 10 | $Et_3N$ (2 equiv), DMF | r.t. | 48 | – | – |
| 6 | **1a + 2a** | Ph | B | 20 | 10 | 10 | $Ph_3P$ (0.54 equiv), $Et_3N$ (2 equiv), DMF | 60–70 | 1.25 | **3a** | 61 |
| 7 | **1a + 2b** | 4-$MeC_6H_4$ | B | 20 | 10 | 10 | $Ph_3P$ (0.54 equiv), $Et_3N$ (2 equiv), DMF | 60–70 | 1 | **3b** | 60[a] |
| 8 | **1a + 2c** | 4-$FC_6H_4$ | B | 20 | 10 | 10 | $Ph_3P$ (0.54 equiv), $Et_3N$ (2 equiv), DMF | 60–70 | 1.25 | **3c** | 56 |
| 9 | **1a + 2f** | Bu | B | 20 | 10 | 10 | $Ph_3P$ (0.54 equiv), $Et_3N$ (2 equiv), DMF | 60–70 | 2 | **3f** | 65 |
| 10 | **1a + 2h** | $CH_2OH$ | B | 20 | 10 | 10 | $Ph_3P$ (0.54 equiv), $Et_3N$ (2 equiv), DMF | 60–70 | 10 | – | – |
| 11 | **1a + 2b** | 4-$MeC_6H_4$ | | 20 | 10 | 10 | $Ph_3P$ (0.54 equiv), $Et_3N$ | 60–70 | 24 | –[b] | –[b] |
| 12 | **1b + 2a** | Ph | C[1] | 10 | 2 | 1.5 | $Et_3N$ | 55–60 | 1 | **3a** | 80 |
| 13 | **1b + 2b** | 4-$MeC_6H_4$ | C[1] | 10 | 2 | 1.5 | $Et_3N$ | 55–60 | 1 | **3b** | 72 |
| 14 | **1b + 2d** | 2-$H_2NC_6H_4$ | C[1] | 20 | 2 | 1.4 | $Et_3N$ | 55–60 | 1 | **3d** | 62 |
| 15 | **1b + 2e** | 2-$(EtO_2CNH)C_6H_4$ | C[1] | 10 | 2 | 1.5 | $Et_3N$ | 55–60 | 1 | **3e** | 88 |
| 16 | **1b + 2f** | Bu | C[1] | 10 | 3 | 1.5 | $Et_3N$ | 55–60 | 2 | **3f** | 79 |
| 17 | **1b + 2g** | $SiMe_3$ | C[1] | 10 | 3 | 2.3 | $Et_3N$ | 55–60 | 1 | **3g** | 67 |
| 18 | **1b + 2f** | Bu | C[2] | 10 | 3 | 1.5 | $Et_3N$[c] | r.t. | 3 | **3f** | 78 |
| 19 | **1b + 2h** | $CH_2OH$ | C[2] | 10 | 3 | 1.5 | $Et_3N$[c] | r.t. | 2.5 | **3h** | 31 |
| 20 | **1b + 2h** | $CH_2OH$ | C[3] | 10 | 3 | 10 | $Et_3N$[c] | r.t. | 1 | **3h** | 33 |
| 21 | **1b + 2h** | $CH_2OH$ | D | 20 | 6 | 1.5 | $Na_2CO_3$ (2 equiv), THF | r.t. | 1.5 | **3h** | 47 |

[a] Diyne **4** (R = 4-$MeC_6H_4$) was isolated in 15% yield.
[b] Diyne **4** (R = 4-$MeC_6H_4$) was the main product (TLC data).
[c] To increase a solubility of the reaction components, 2–3 drops DMF were added.

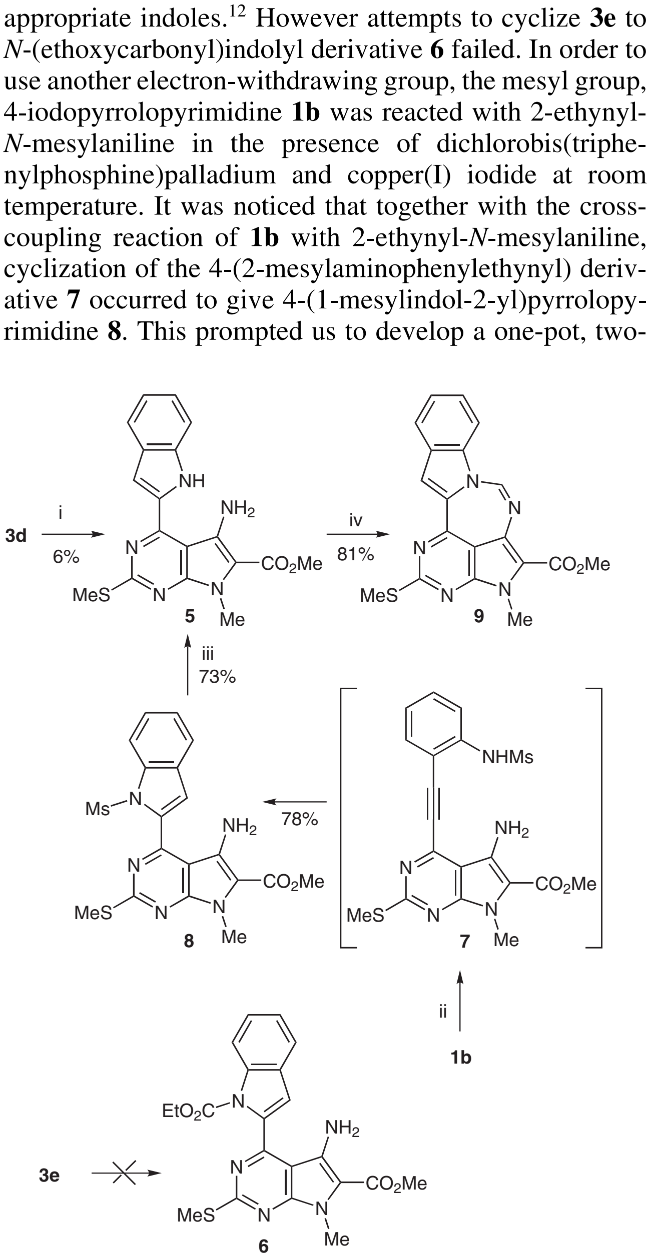
was obtained by reaction of **1a** with 67% hydroiodic acid in acetone. The cross-coupling reaction of 4-iodopyrrolopyrimidine **1b** with different alkynes proceeded more smoothly when compared with that of 4-chloropyrrolopyrimidine **1a**. According to TLC data the formation of diynes **4** also occurred during the reaction of **1b** with alkynes, but in negligible quantities, thus the use of 1.4–2.3 equivalents of alkyne was sufficient to achieve full conversion of **1b**. Furthermore, the cross-coupling reaction of **1b** with different alkynes to give the corresponding 4-alkynylpyrrolopyrimidines **3a**,**b**,**d**–**g** proceeded well with smaller quantities of copper(I) iodide (10 mol%) and dichlorobis(triphenylphosphine)palladium (2–3 mol%) and without the addition of triphenylphosphine (method $C^1$, entries 12–17). 4-Hex-1-ynylpyrrolopyrimidine **3f** was also obtained from **1b** at room temperature (Method $C^2$, entry 18). Experiments directed to find optimal conditions for the synthesis of 4-(2-hydroxyprop-1-ynyl)pyrrolopyrimidine derivative **3h** revealed that performing the reactions at room temperature also gives better results. A larger excess of prop-2-yn-1-ol shortened the conversion time of the substrate **1b**, but did not affect the yield of **3h** (entries 19, 20). At higher temperatures the cross-coupling reaction of **1b** with alkyne **2h** proceeded ambiguously. Complex inseparable mixtures of products were formed. Nevertheless, the best result for the synthesis of **3h** was obtained when the reaction was carried out in tetrahydrofuran in the absence of triphenylphosphine and using sodium carbonate as a base (entry 21).

Among the most efficient procedures for indole 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[10] and, more recently, copper salts.[11] Since **3d** could serve as a key intermediate for the synthesis of the indole moiety in the position 4 of pyrrolopyrimidine, it was of interest to examine two possible routes for the synthesis of **3d** from **1b** (Scheme 2). In the first route, 4-trimethylsilyl derivative **3g**, obtained from **1b** as described above (Table 1, entry 17), was desilylated to give 4-ethynylpyrrolopyrimidine **3i** using potassium fluoride in the presence of dicyclohexano-18-crown-6. However, reaction of **3i** under the Sonogashira conditions with 2-iodoaniline gave a complex mixture of products from which the target compound **3d** was isolated only in 11% yield. Alternatively, **3d** was obtained in 62% yield by cross-coupling reaction of **1b** with 2-ethynylaniline (**2d**) using 2 mol% dichlorobis(triphenylphosphine)palladium and 20 mol% copper(I) iodide in triethylamine at 55–60 °C (Table 1, entry 14).

An attempt to synthesize 4-indolylpyrrolopyrimidine **5** by reaction of **3d** with copper(I) iodide in *N*,*N*-dimethylformamide at 100 °C led to a complex reaction mixture, from which the desired compound **5** was isolated only in 6% yield (Scheme 3).[8] It is known that electron-withdrawing groups such as mesyl, acetyl, trifluoroacetyl, or ethoxycarbonyl groups attached to the amino group of 2-ethynylanilines often facilitate their cyclization into the appropriate indoles.[12] However attempts to cyclize **3e** to *N*-(ethoxycarbonyl)indolyl derivative **6** failed. In order to use another electron-withdrawing group, the mesyl group, 4-iodopyrrolopyrimidine **1b** was reacted with 2-ethynyl-*N*-mesylaniline in the presence of dichlorobis(triphenylphosphine)palladium and copper(I) iodide at room temperature. It was noticed that together with the cross-coupling reaction of **1b** with 2-ethynyl-*N*-mesylaniline, cyclization of the 4-(2-mesylaminophenylethynyl) derivative **7** occurred to give 4-(1-mesylindol-2-yl)pyrrolopyrimidine **8**. This prompted us to develop a one-pot, two-




**Scheme 2** *Reagents and conditions*: (i) KF·2 $H_2O$, dicyclohexano-18-crown-6, $CH_2Cl_2$, r.t., 15 min; (ii) 2-iodoaniline, $PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), $Et_3N$, 55–60 °C, 3 h.




**Scheme 3** *Reagents and conditions*: (i) CuI (2 equiv), DMF, 100 °C, 12 h; (ii) 1. 2-ethynyl-*N*-mesylaniline (1.2 equiv), $PdCl_2(PPh_3)_2$ (10 mol%), CuI (0.5 equiv), $Et_3N$, DMF, r.t., 3 h; 2. CuI (1.5 equiv), 50–60 °C, 3 h; (iii) KOH, MeOH, reflux, 25 min; (iv) $HC(OEt)_3$, $NH_4Cl$, 100–110 °C, 8 h.

step synthesis of **8** from 4-iodopyrrolopyrimidine **1b**; when coupling reaction at room temperature between **1b** and 2-ethynyl-*N*-mesylaniline was complete an additional amount of copper(I) iodide was added and the reaction temperature was raised to 50–60 °C. 4-(1-Mesylindol-2-yl)pyrrolopyrimidine **8** was isolated in 78% yield.[8] *N*-Mesyl derivative **8** was deprotected to give 4-(indol-2-yl)pyrrolopyrimidine **5** on heating with potassium hydroxide in methanol.[8]

Heating **5** with excess ethyl orthoformate at 100–110 °C in the presence of ammonium chloride furnished methyl 4-methyl-2-(methylsulfanyl)-4*H*-pyrrolo[2,3,4-*de*]pyrimido[5′,4′:5,6][1,3]diazepino[1,7-*a*]indole-5-carboxylate (**9**), a representative of a fused heterocycle containing the biologically important pyrrolopyrimidine, 1,3-diazepine, and indole moieties.[8]

In conclusion, this investigation provides access to novel 4-alkynylpyrrolo[2,3-*d*]pyrimidines that are useful precursors for biologically active compounds and more complex fused heterocycles.

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls or in KBr discs on a Perkin-Elmer FTIR spectrophotometer Spectrum BX II. $^1$H NMR spectra were recorded with a Varian Unity spectrometer (300 MHz). The MS spectrum was obtained on a LC-ESI-MS spectrometer Agilent 1100 MSD using $H_2O$–MeOH as solvent at 25 °C (positive scan 50–600 *m*/*z*, fragmentator 70 eV). Elemental analyses (C, H, N) were performed at the Elemental Analysis Laboratory of the Department of Organic Chemistry of Vilnius University. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 $F_{254}$ aluminum plates (Merck). Visualization was accomplished by UV light.

Synthetic procedures, spectral, and analytical data for methyl 5-amino-7-methyl-2-(methylsulfanyl)-4-[1-(methylsulfonyl)-1*H*-indol-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (**8**) and methyl 4-methyl-2-(methylsulfanyl)-4*H*-pyrrolo[2,3,4-*de*]pyrimido[5,′4′:5,6][1,3]diazepino[1,7-*a*]indole-5-carboxylate (**9**) are detailed in our preliminary report.[8]

**Methyl 5-Amino-4-iodo-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (1b)**

To a mixture, prepared by slow addition of 67% HI (15 mL) to acetone (15 mL), was added **1a**[9] (1.5 g, 5.23 mmol). The mixture was stirred at r.t. for 8 h, then poured onto ice (24 g) and 20% NaOH soln (33 mL) was added. The mixture was stirred for 2–5 h until the color of precipitate became bright yellow. The solid was filtered, dried, and recrystallized (*i*-PrOH) to give **1b** (1.8 g, 91%); mp 160.5–161 °C.[8]

IR (Nujol): 3462, 3352 ($NH_2$), 1681 cm$^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, $SCH_3$), 3.88 (s, 3 H, $NCH_3$), 3.94 (s, 3 H, $OCH_3$), 5.70 (s, 2 H, $NH_2$).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.7, 31.0, 51.5, 107.5, 109.9, 121.6, 136.4, 148.8, 163.3, 168.6.

Anal. Calcd for $C_{10}H_{11}IN_4O_2S$ (378.19): C, 31.76; H, 2.93; N, 14.81. Found: C, 31.45; H, 2.85; N, 14.98.

**Methyl 5-Amino-7-methyl-2-(methylsulfanyl)-4-(phenylethynyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3a); Typical Procedures**

*Method A*: Argon was bubbled through a mixture of **1a** (0.2 g, 0.7 mmol), CuI (26 mg, 0.14 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 mL) for 10 min. Then phenylacetylene (**2a**, 0.7 g, 6.96 mmol) was added dropwise. The mixture was stirred at r.t. for 18 h and then cooled to –5 °C. The precipitate was filtered off, washed with cold *i*-PrOH and recrystallized (*i*-PrOH) to give **3a** (0.16 g, 65%); mp 180–181.5 °C.

*Method B*: Argon was bubbled through a mixture of **1a** (0.2 g, 0.7 mmol), CuI (26 mg, 0.14 mmol), $Ph_3P$ (0.1 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 mL) for 10 min. Then phenylacethylene (**2a**, 0.7 g, 6.96 mmol) was added dropwise at 60–70 °C (bath temperature). The mixture was stirred at 60–70 °C for 75 min and then cooled to –5 °C. The precipitate was filtered off, washed with cold *i*-PrOH and recrystallized (*i*-PrOH) to give **3a** (0.15 g, 61%); mp 180–181.5 °C.

*Method C$^1$*: Argon was bubbled through a mixture of **1b** (0.2 g, 0.53 mmol), CuI (10 mg, 0.054 mmol), $PdCl_2(PPh_3)_2$ (8 mg, 0.0114 mmol), and $Et_3N$ (10 mL) for 10 min. The mixture was heated to 50 °C (bath temperature) and then phenylacetylene (**2a**, 84 mg, 0.82 mmol) was added dropwise. The mixture was stirred under argon at 55–60 °C for 1 h. After cooling to r.t. the precipitate was collected by filtration and recrystallized (*i*-PrOH) to give **3a** (0.15 g, 80%); mp 180–181.5 °C.

IR (Nujol): 3426, 3331 ($NH_2$), 2211 (C≡C), 1675 cm$^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, $SCH_3$), 3.91 (s, 3 H, $NCH_3$), 3.95 (s, 3 H, $OCH_3$), 5.63 (s, 2 H, $NH_2$), 7.41–7.52 (m, 3 H, Ar-H), 7.65–7.68 (m, 2 H, Ar-H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 30.8, 51.45, 86.1, 97.1, 106.7, 107.5, 121.1, 129.0, 130.5, 132.5, 136.1, 143.6, 150.7, 163.4, 169.7.

Anal. Calcd for $C_{18}H_{16}N_4O_2S$ (352.41): C, 61.35; H, 4.58; N, 15.90. Found: C, 61.22; H, 4.35; N, 15.61.

**Methyl 5-Amino-7-methyl-4-[(4-methylphenyl)ethynyl]-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3b)**

Following the typical procedures for methods A and C$^1$ gave **3b**; yield: 70% (method A), 72% (method C$^1$); mp 157–158.5 °C (MeCN).

Compound **3b** was also obtained using the typical procedure for method B, using **1a** (0.2 g, 0.7 mmol) and (4-methylphenyl)acetylene (**2b**, 0.8 g, 6.95 mmol). The product was isolated as follows: After cooling the mixture to –5 °C, the precipitate was collected by filtration, washed with cold *i*-PrOH and purified by column chromatography (silica gel, $CHCl_3$) to give di(4-methylphenyl)buta-1,3-diyne (**4b**) (0.12 g, 15%); mp 180–181 °C (BuOH) [Lit.[13] 183 °C]; $R_f$ = 0.5 ($CHCl_3$); and **3b** (0.15 g, 60%); mp 157–158.5 °C (MeCN); $R_f$ = 0.4 ($CHCl_3$).

IR (Nujol): 3435, 3337 ($NH_2$), 2198 (C≡C), 1670 cm$^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, $CH_3$), 2.66 (s, 3 H, $SCH_3$), 3.92 (s, 3 H, $NCH_3$), 3.96 (s, 3 H, $OCH_3$), 5.65 (s, 2 H, $NH_2$), 7.25 (d, $J_{3'-2'}$ = 7.9 Hz, 2 H, H3′, H5′), 7.56 (d, $J_{2'-3'}$ = 7.9 Hz, 2 H, H2′, H6′).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 22.0, 30.8, 51.45, 85.7, 97.7, 106.6, 107.4, 118.0, 129.75, 132.5, 136.2, 141.1, 143.9, 150.7, 163.4, 169.7.

Anal. Calcd for $C_{19}H_{18}N_4O_2S$ (366.44): C, 62.28; H, 4.95; N, 15.29. Found: C, 62.12; H, 4.95; N, 14.90.

**Methyl 5-Amino-4-[(4-fluorophenyl)ethynyl]-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3c)**

Following the typical procedures for methods A and B gave **3c**; yield: 58% (method A), 56% (method B); mp 193–194.5 °C (*i*-

PrOH).

IR (Nujol): 3436, 3343 ($NH_2$), 2205 (C≡C), 1670 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, $SCH_3$), 3.90 (s, 3 H, $NCH_3$), 3.94 (s, 3 H, $OCH_3$), 5.60 (s, 2 H, $NH_2$), 7.10–7.17 (m, 2 H, Ar-H), 7.63–7.70 (m, 2 H, Ar-H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 30.8, 51.5, 85.9, 96.0, 106.7, 107.6, 116.5 (d, $J_{3'\text{-F}}$, $J_{5'\text{-F}}$ = 23.1 Hz, C3′, C5′), 117.2, 134.65 (d, $J_{2'\text{-F}}$, $J_{6'\text{-F}}$ = 8.5 Hz, C2′, C6′), 136.0, 143.5, 150.7, 163.4, 163.9 (d, $J_{4'\text{-F}}$ = 252.7 Hz, C4′), 169.7.

Anal. Calcd for $C_{18}H_{15}FN_4O_2S$ (370.41): C, 58.37; H, 4.08; N, 15.13. Found: C, 58.12; H, 4.13; N, 14.99.

**Methyl 5-Amino-4-[(2-aminophenyl)ethynyl]-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3d)**

*From **3i** and 2-iodoaniline*: Argon was bubbled through a mixture of 2-iodoaniline (44 mg, 0.2 mmol), CuI (7 mg, 0.037 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and $Et_3N$ (5 mL) for 10 min. The mixture was heated to 50 °C and **3i** (60 mg, 0.22 mmol) was added. The mixture was stirred at 55–60 °C (bath temperature) for 3 h, then cooled to r.t. and diluted with $CH_2Cl_2$. Solvents were evaporated under reduced pressure and the residue was purified using dry column vacuum chromatography[14] (silica gel 5–40 μ, $CHCl_3$) to give **3d** (8 mg, 11%); mp 225–228 °C ($CHCl_3$).

*From **1b** and **2d** by method $C^1$*: Alternatively, following the typical procedure for method C[1] using **1b** (0.4 g, 1.06 mmol), CuI (40 mg, 0.21 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol), and 2-ethynylaniline[10c] (**2d**, 0.17 g, 1.45 mmol) gave **3d** (0.24 g, 62%); mp 227–230 °C ($CHCl_3$).

IR (Nujol): 3491, 3387, 3311, 3214 (2 $NH_2$), 2193 (C≡C), 1699 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, $SCH_3$), 3.92 (s, 3 H, $NCH_3$), 3.95 (s, 3 H, $OCH_3$), 4.50 (s, 2 H, $C_6H_4NH_2$), 5.64 (s, 2 H, 5-$NH_2$), 6.73–6.79 (m, 2 H, Ar-H), 7.23–7.27 (m, 1 H, Ar-H), 7.43–7.46 (m, 1 H, Ar-H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 30.8, 51.5, 91.6, 94.9, 105.4, 106.5, 107.5, 115.1, 118.4, 132.1, 133.1, 136.0, 143.8, 149.6, 150.7, 163.4, 169.6.

Anal. Calcd for $C_{18}H_{17}N_5O_2S$ (367.42): C, 58.84; H, 4.66; N, 19.06. Found: C, 58.92; H, 4.67; N, 18.68.

**Methyl 5-Amino-4-{[2-(ethoxycarbonylamino)phenyl]ethynyl}-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3e)**

Following the typical procedure for method C[1] using **1b** (0.45 g, 1.19 mmol), CuI (23 mg, 0.12 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 0.026 mmol), and ethyl *N*-(2-ethynylphenyl)carbamate[15] (**2e**, 0.33 g, 1.75 mmol) gave **3e** (0.46 g, 88%); mp 179.5–180.5 °C (EtOH).

IR (KBr): 3487, 3378, 3289 ($NH_2$, NH), 2206 (C≡C), 1739, 1705 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_3$), 2.67 (s, 3 H, $SCH_3$), 3.92 (s, 3 H, $NCH_3$), 3.96 (s, 3 H, $OCH_3$), 4.30 (q, *J* = 7.2 Hz, 2 H, $CH_2$), 5.53 (s, 2 H, $NH_2$), 7.11–7.13 (m, 1 H, Ar-H), 7.47–7.49 (m, 1 H, Ar-H), 7.58–7.61 (m, 2 H, Ar-H, NH), 8.25 (d, *J* = 8.1 Hz, 1 H, Ar-H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 14.8, 30.9, 51.6, 61.9, 92.37, 92.40, 106.9, 108.1, 109.5, 119.0, 123.1, 132.0, 132.9, 135.7, 140.6, 143.1, 150.7, 153.5, 163.3, 169.6.

Anal. Calcd for $C_{21}H_{21}N_5O_4S$ (439.49): C, 57.39; H, 4.82; N, 15.92. Found: C, 57.53; H, 5.15; N, 15.58.

**Methyl 5-Amino-4-hex-1-ynyl-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3f)**

Following the typical procedure for methods B, C[1] and C[2], **3f** was isolated by the following procedure: When the reaction was complete, the solvents were evaporated under reduced pressure and the residue was purified using dry column vacuum chromatography[14] (silica gel 5–40 μ, $CHCl_3$) to give **3f**; yield: 65% (method B), 79% (method C[1]), 78% (Method C[2]); mp 117–118.5 °C (hexane).

IR (Nujol): 3471, 3344 ($NH_2$), 2223 (C≡C), 1672 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.987 (t, *J* = 7.27 Hz, 3 H, $CH_2CH_3$), 1.47–1.59 (m, 2 H, $CH_2CH_3$), 1.66–1.76 (m, 2 H, $CH_2CH_2CH_3$), 2.59 (t, *J* = 7.13 Hz, 2 H, C≡$CCH_2$), 2.61 (s, 3 H, $SCH_3$), 3.87 (s, 3 H, $NCH_3$), 3.93 (s, 3 H, $OCH_3$), 5.57 (s, 2 H, $NH_2$).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.5, 19.7, 22.4, 30.4, 30.7, 51.4, 78.3, 100.2, 106.6, 107.0, 136.3, 144.2, 150.7, 163.4, 169.6.

Anal. Calcd for $C_{16}H_{20}N_4O_2S$ (332.43): C, 57.81; H, 6.06; N, 16.85. Found: C, 58.27; H, 6.00; N, 16.64.

**Methyl 5-Amino-7-methyl-2-(methylsulfanyl)-4-[(trimethylsilyl)ethynyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3g)**

Following the typical procedure for method C[1], with isolation as for **3f**; yield: **3g** (67%); mp 127–130 °C. Compound **3g** was sufficiently pure to use in the synthesis of **3i**; it decomposed partially during crystallization.

IR (Nujol): 3484, 3398, 3364 ($NH_2$), 2161 (C≡C), 1672 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.33 [s, 9 H, $Si(CH_3)_3$], 2.62 (s, 3 H, $SCH_3$), 3.89 (s, 3 H, $NCH_3$), 3.94 (s, 3 H, $OCH_3$), 5.61 (br s, 2 H, $NH_2$).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = –0.4, 14.6, 30.7, 51.4, 100.9, 104.6, 106.8, 107.3, 135.9, 143.1, 150.7, 163.3, 169.7.

MS (ES+): *m*/*z* = 349 (M + 1).

**Methyl 5-Amino-4-(3-hydroxyprop-1-ynyl)-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3h)**

*Method $C^2$*: Argon was bubbled through a suspension of **1b** (0.2 g, 0.53 mmol), CuI (10 mg, 0.054 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.0157 mmol), $Et_3N$ (4 mL), and DMF (3 drops) for 10 min. Propynol (**2h**, 45 mg, 0.8 mmol) was added and the mixture was stirred at r.t. under argon for 2.5 h. The mixture was poured into $H_2O$ and the product was extracted with $CH_2Cl_2$. Solvents were evaporated under reduced pressure and the residue was purified using dry column vacuum chromatography[14] (silica gel 5–40 μ, $CH_2Cl_2$). The obtained product was recrystallized ($CHCl_3$, –5 °C) to give **3h** (50 mg, 31%); mp 173–174.5 °C.

*Method $C^3$*: Compound **3h** was synthesized analogously to method C[2] with the difference that propynol (10 equiv) was used. The reaction time, 1 h. Yield: 33%; mp 173–174.5 °C ($CHCl_3$).

*Method D*: To a suspension of **1b** (0.1 g, 0.26 mmol), CuI (10 mg, 0.054 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.0157 mmol), and $Na_2CO_3$ (56 mg, 0.53 mmol) in THF (5 mL) was added propynol (**2h**, 22 mg, 0.39 mmol). The mixture was stirred at r.t. under argon for 1.5 h, then the mixture was filtered through a layer of silica gel (Fluka Silica Gel 60, $Et_2O$). $Et_2O$ was removed, the residue washed with cold $Et_2O$ and recrystallized ($CHCl_3$, –5 °C) to give **3h** (38 mg, 47%); mp 173–174.5 °C.

IR (Nujol): 3475, 3364 ($NH_2$), 3165 (OH), 2233 (C≡C), 1672 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.3 (t, $J_{\text{OH-3}}$ = 6.60 Hz, 1 H, OH), 2.64 (s, 3 H, $SCH_3$), 3.91 (s, 3 H, $NCH_3$), 3.96 (s, 3 H, $OCH_3$), 4.65 (d, $J_{\text{3-OH}}$ = 6.60 Hz, 2 H, $CH_2$), 5.59 (s, 2 H, $NH_2$).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 30.8, 51.5, 51.7, 82.3, 96.0, 106.6, 107.4, 135.9, 142.9, 150.5, 163.4, 169.5.

Anal. Calcd for $C_{13}H_{14}N_4O_3S$ (306.35): C, 50.97; H, 4.61; N, 18.29. Found: C, 51.20; H, 4.42; N, 18.01.

**Methyl 5-Amino-4-ethynyl-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (3i)**

To a soln of **3g** (0.5 g, 1.44 mmol) and dicyclohexano-18-crown-6 (0.55 g, 1.48 mmol) in $CH_2Cl_2$ (20 mL) was added $KF·2H_2O$ (0.35 g, 3.72 mmol). The mixture was stirred at r.t. for 15 min, then poured into $H_2O$ and extracted with $CH_2Cl_2$. The solvents were removed from the combined organic extracts under reduced pressure to give a solid that was washed with $Et_2O$ and recrystallized (*i*-PrOH) to give **3i** (0.33 g, 82%); mp 172–174 °C.

IR (Nujol): 3486, 3440, 3343 ($NH_2$), 2111 (C≡C), 1673 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, $SCH_3$), 3.65 (s, 1 H, C≡CH), 3.87 (s, 3 H, $NCH_3$), 3.94 (s, 3 H, $OCH_3$), 5.57 (s, 2 H, $NH_2$).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 30.8, 51.5, 80.3, 84.7, 107.0, 107.5, 135.7, 142.3, 150.6, 163.3, 169.6.

Anal. Calcd for $C_{12}H_{12}N_4O_2S$ (276.32): C, 52.16; H, 4.38; N, 20.28. Found: C, 51.89; H, 4.51; N, 19.99.

**Methyl 5-Amino-4-(1*H*-indol-2-yl)-7-methyl-2-(methylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (5)**

*Method E*: A mixture of **3d** (50 mg, 0.14 mmol), DMF (5 mL), and CuI (52 mg, 0.28 mmol) was stirred at 100 °C for 12 h, then evaporated under reduced pressure to dryness. The residue was purified by column chromatography (silica gel, $CHCl_3$) to give **5** (3 mg, 6%); mp 172–174 °C (*i*-PrOH).

*Method F*:[8] To boiling 5% KOH in MeOH (25 mL) was added **8** (50 mg, 0.11 mmol). The mixture was refluxed for 25 min, then cooled to r.t., poured into $H_2O$ and extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. The solid was recrystallized (*i*-PrOH) to give **5** (30 mg, 73%); mp 172–174 °C.

IR (Nujol): 3428, 3335 ($NH_2$), 1696 $cm^{-1}$ (CO).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H, $SCH_3$), 3.96 (s, 3 H, $NCH_3$), 3.98 (s, 3 H, $OCH_3$), 5.59 (s, 2 H, $NH_2$), 7.20 (ddd, $J$ = 0.9 Hz, $J_{5'-6'}$ = 7.0 Hz, $J_{5'-4'}$ = 7.9 Hz, 1 H, H5′), 7.35 (ddd, $J$ = 1 Hz, $J_{6'-5'}$ = 7.0 Hz, $J_{6'-7'}$ = 8.3 Hz, 1 H, H6′), 7.52–7.47 (m, 2 H, H3′, H7′), 7.73 (dd, $J$ = 0.7 Hz, $J_{4'-5'}$ = 7.9 Hz, 1 H, H4′), 9.6 (s, 1 H, NH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.6, 31.1, 51.5, 102.8, 107.3, 108.2, 112.0, 120.9, 122.1, 125.0, 128.8, 134.1, 136.3, 137.0, 151.9, 152.8, 163.6, 168.3.

Anal. Calcd for $C_{18}H_{17}N_5O_2S$ (367.43): C, 58.84; H, 4.66; N, 19.06. Found: C, 58.54; H, 4.72; N, 19.21.

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