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-sulfanyl-7H-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 as well as an important functional moiety in a wide range of biologically active compounds. The development of methods for the introduction of the alkynyl group into organic molecules is an important target. For this purpose the Sonogashira reaction has enjoyed tremendous success because of its mild reaction conditions and great tolerance to nearly all types of functional groups. 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. Nevertheless the Sonogashira reaction in the pyrrolo[2,3-d]pyrimidine series has not, as yet, been extensively studied. 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 and no work has been done with pyrrolo[2,3-d]pyrimidines bearing halo groups in the pyrimidine moiety. Recently in our preliminary report, we have shown that under the Sonogashira reaction conditions 5-amino-4-halo-2-(methylsulfanyl)pyrrolo[2,3-d]pyrimidine-6-carboxylates and aroylacetylenes 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)-7H-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; 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).

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

Scheme 1

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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.

### 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>R</th>
<th>Method</th>
<th>CuI (mol%)</th>
<th>PdCl₂(PPh₃)₂ (mol%)</th>
<th>Alkyne (equiv)</th>
<th>Base, solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product Yield (%)</th>
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<td>1a + 2a</td>
<td>Ph</td>
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<td>Na₂CO₃ (2 equiv), THF</td>
<td>1.5</td>
<td>3h 47</td>
<td></td>
</tr>
</tbody>
</table>

* Diyne 4 (R = 4-MeC₆H₄) was isolated in 15% yield.
* Diyne 4 (R = 4-MeC₆H₄) was the main product (TLC data).
* 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 gave 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 C1, entries 12–17). 4-Hex-1-ynylpyrrolopyrimidine was also obtained from C1, entries 12–17). 4-Hex-1-ynylpyrrolopyrimidine 3f was also obtained from 1b at room temperature (Method C2, 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 complexes10 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-stage reaction of 4-iodopyrrolopyrimidine 1b with 2-ethynyl-N-mesylaniline (Scheme 2).

**Scheme 3** Reagents and conditions: (i) CuI (2 equiv), DMF, 100 °C, 12 h; (ii) 2-ethynyl-N-mesylaniline (1.2 equiv), PdCl2(PPh3)2 (10 mol%), CuI (0.5 equiv), EtN, DMF, r.t., 3 h; (ii) CuI (1.5 equiv), 50–60 °C, 3 h; (iii) KOH, MeOH, reflux, 25 min; (iv) HC(OEt)3, NH4Cl, 100–110 °C, 8 h.

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step synthesis of 8 from 4-iodopyrrolopyrimidine 1b; when coupling reaction at room temperature between 1b and 2-ethyl-N-3 mesylaniline was complete an additional amount of copper(I) iodide was added and the reaction temperature was raised to 50–60 °C. 4-(1-Mesitylindol-2-yl)pyrrolopyrimidine 8 was isolated in 78% yield. N-MesyI derivative 8 was deprotected to give 4-(indol-2-yl)pyrrolopyrimidine 5 on heating with potassium hydroxide in methanol.

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

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. 1H 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 H2O–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 F254 aluminum plates (Merek). Visualization was accomplished by UV light.

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

**Methyl 5-Amino-4-ido-2-(methylsulfanyl)-7H-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 9 (1.5 g, 5.23 mmol). The product was isolated as follows: After cooling the mixture to –5 °C, the precipitate was collected by filtration and recrystallized (i-PrOH) to give 1b (1.8 g, 91%); mp 160.5–161 °C.1

IR (Nujol): 3462, 3352 (NH2), 1681 cm–1 (CO).

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

A mixture, prepared by slow addition of 67% HI (15 mL) to acetone (15 mL), was added 9 (1.5 g, 5.23 mmol). The mixture was stirred for 2–5 h until the color of precipitate became bright yellow. The solid was filtered, washed with cold -PrOH and recrystallized (i-PrOH) to give 3a (1.0 g, 83%); mp 193–194.5 °C (i-PrOH).

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

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

**Methyl 5-Amino-7-methyl-2-(methylsulfanyl)ethynyl-2-(methylsulfanyl)-7H-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.

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PdCl2(PPh3)2 (14 mg, 0.02 mmol), and Et3N (5 mL) for 10 min. The mixture was stirred at 55–60 °C (bath temperature) for 3 h, then heated to 50 °C and kept for 6 h. The mixture was poured into H2O and the residue washed with cold CH2Cl2. Solvents were evaporated under reduced pressure and the residue was purified using dry column vacuum chromatography14 (silica gel 5–40 Å, CHCl3) to give 3d (method C1), 78% (Method C2); mp 117–118.5 °C (hexane). Anal. Calcd for C18H15FN4O2S (370.41): C, 58.37; H, 4.08; N, 19.06; S, 19.59. Found: C, 58.3; H, 4.1; N, 19.1.

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

Following the typical procedure for method C1, with isolation as for 3f; yield: 3g (67%); mp 127–130 °C. Compound 3g was sufficiently pure to use in the synthesis of 3h; it decomposed partially during crystallization.

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

**Method C3:** Argon was bubbled through a suspension of 1b (0.2 g, 0.53 mmol), Cu(0.1 g, 0.26 mmol), and CH2Cl2. The mixture was stirred at r.t. under argon for 2.5 h. The mixture was poured into H2O and the residue was extracted with CH2Cl2. Solvents were evaporated under reduced pressure and the residue was purified using dry column vacuum chromatography14 (silica gel 5–40 Å, CHCl3). The obtained product was recrystallized (CHCl3, –5 °C) to give 3h (50 mg, 31%); mp 173–174.5 °C. Anal. Calcd for C18H15FN4O2S (370.41): C, 58.37; H, 4.08; N, 19.06; S, 19.59. Found: C, 58.3; H, 4.1; N, 19.1.

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

Following the typical procedure for methods B, C1 and C2, 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 chromatography14 (silica gel 5–40 Å, CHCl3) to give 3f; yield: 65% (method B), 79% (method C2), 78% (Method C3); mp 117–118.5 °C (hexane). Anal. Calcd for C18H15FN4O2S (370.41): C, 58.37; H, 4.08; N, 19.06; S, 19.59. Found: C, 58.3; H, 4.1; N, 19.1.
Methyl 5-Amino-4-ethyl-7-methyl-2-(methylsulfonyl)-7H-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 \( \text{CH}_2\text{Cl}_2 (20 \text{ mL}) \) was added \( \text{KF} \cdot 2\text{H}_2\text{O} (0.35 \text{ g}, 3.72 \text{ mmol}) \). The mixture was stirred at rt. for 15 min, then poured into \( \text{H}_2\text{O} \) and extracted with \( \text{CH}_2\text{Cl}_2 \). The solvents were removed from the combined organic extracts under reduced pressure to give a solid that was washed with EtOAc and recrystallized (i-PrOH) to give 3i (0.33 g, 82%); mp 172–174 °C.

IR (Nujol): 3428, 3335 (NH2), 1696 cm–1 (CO).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.62 \text{ (s, 3 H, SCH\(_2\))}, 3.65 \text{ (s, 1 H, C=CH)}, 3.87 \text{ (s, 3 H, NCH\(_3\))}, 3.94 \text{ (s, 3 H, OCH\(_3\))}, 5.57 \text{ (s, 2 H, NH\(_2\))}.

\(^1\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 14.6, 30.8, 51.5, 80.3, 84.7, 107.0, 107.5, 135.7, 142.3, 150.6, 163.3, 169.6.


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References


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