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Efficient synthesis of aminomethylated azaindoles and corresponding pyrrole-fused derivatives by copper-catalyzed domino multicomponent coupling and cyclization

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Abstract
Efficient methods for the synthesis of aminomethylated azaindole derivatives via domino copper-catalyzed multicomponent coupling and cyclization have been developed. Using various secondary amines and aldehydes, \(N\)-substituted 3-ethynyl-4-aminopyridine was converted to substituted azaindoles in moderate to excellent yields. By use of a 3,4-diaminopyridine derivative bearing two alkynyl groups, the corresponding pyrrole-fused azaindoles were synthesized by controlled stepwise cyclization.

Keywords:
CK2 inhibitor
Multi-component reaction
Azaindole
Regioselective
Pyrrole-fused azaindole

1. Introduction
Azaindoles and related heteroaromatic ring systems are common scaffolds in biologically active natural and synthetic compounds. Their widespread application as pharmaceutical agents makes them attractive synthetic targets. Several synthetic routes to access azaindoles are described in the literature, most of which rely on linear synthesis utilizing the conventional cyclization of ortho-amino-alkynyl pyridines promoted by bases or transition metals. However, few methods have been reported for azaindole synthesis based on multiple component reactions, which provide a divergent approach to functionalized azaindoles in a single step.

We recently reported the direct synthesis of 2-(aminomethyl)indoles via copper-catalyzed domino three-component coupling and cyclization reactions of ethynylaniline 1 (Scheme 1). The mechanism of this reaction involves the formation of the propargylamine intermediate by Mannich-type three-component coupling of 1 with paraformaldehyde and a secondary amine, and subsequent copper-catalyzed intramolecular cyclization. Using a modified protocol, we developed an efficient synthesis of a series of aminomethylated dipyroloarenes by direct bicyclization.

As a part of our ongoing project directed toward development of novel CK2 inhibitors, we designed aminomethylated azaindole derivatives and more complicated pyrrole-fused azaindole derivatives as potential drug-like templates. They are considered to be synthesized by a copper-catalyzed three-component coupling and cyclization reaction. Here, we report our research on the synthesis of aminomethylated azaindole derivatives using various aldehydes and secondary amines. The synthesis of corresponding pyrrole-fused derivatives by a controlled stepwise cyclization is also depicted.

2. Results and discussion
We initially designed a synthetic route to and through a common starting material 6 (Scheme 2). The azaindole bearing an aminomethyl group can be directed from their nitro congener 7 by reduction. The nitroazaindole 7 is considered to be synthesized by the copper-catalyzed three-component coupling and cyclization reaction of 6 with various aldehydes and secondary amines. The amino group of 4 is envisioned to facilitate a regioselective ortho-bromination, permitting introduction of an alkynyl group by Sonogashira coupling. Finally, the subsequent intramolecular cyclization would afford the pyrrole-fused azaindoles 5.
In our previous study on three-component indole formation, the intramolecular hydroamination required N-substituted ethynylanilines.\textsuperscript{15,21} Therefore, 3-ethyl-4-aminopyridine 6a having an acetyl group was synthesized (see Experimental 4.2) and applied to optimize the reaction conditions for the domino three-component coupling-cyclization (Table 1). We started our investigation by treating 6a with paraformaldehyde and dipropylamine in dioxane at 80 °C in the presence of 10 mol % CuCl (entry 1). The initial Mannich-type three-component coupling was found to proceed readily to afford 8a by TLC. However, the subsequent intramolecular hydroamination was rather slow to yield the desired cyclization product 7a as the deacetylated form in low yield (40%),\textsuperscript{26} accompanied by the formation of undesired bis-(aminomethyl)side product 9a in 10% yield. Addition of K$_3$PO$_4$ resulted in decomposition of the substrate (entry 2), whereas Et$_3$N slightly improved the yield of 7a (49%, entry 3). According to the previous study, the counteranion of copper catalysts considerably affects the reactivity of the alkyne toward intramolecular hydroamination.\textsuperscript{18,21} Among the copper salts investigated (CuI, CuBr, CuCl, entries 3–5), CuCl afforded the highest yield of 7a (61%, entry 5). Considering that AcOH (resulted in situ from 6a by the deacetylation with water formed in the step of Mannich reaction) might hinder intramolecular hydroamination, we applied MS4A as an additive to remove water and/or AcOH. As hoped, addition of MS4A dramatically accelerated the cyclization rate to yield 7a in 85% yield without formation of the side product 9a (entry 6). Next, we examined the scope of the 2-(aminomethyl)azaindole formation using several secondary amines (entries 7–10). All the secondary amines tested here proved to be acceptable as amine components to yield desired products 7b–7e in high yields (71–86%).

We also investigated the three-component synthesis of 2-(aminomethyl)azaindole using alkyl or aryl aldehydes (Scheme 3). Treating 6a with butanal and piperidine under optimized conditions afforded the three-component coupling intermediate 10a without formation of the desired cyclization product 11a. Instead of Et$_3$N, use of the relatively strong base DBU was effective in promoting the intramolecular hydroamination of 10a. After complete formation of 10a (monitored by TLC), DBU (2 equiv) was added to the reaction mixture to give the desired azaindole 11a in 68% yield in a one-pot manner (eq 1). Meanwhile, treatment of 6a with benzaldehyde and piperidine under standard conditions afforded the three-component coupling intermediate 10b in 59% yield, mixed with an inseparable co-product 12 in 18% yield. Although treatment of this mixture even after isolation with DBU was ineffective (leading to formation of undesired 1,6-naphthyridine 13 in 60% yield), replacement of DBU with K$_3$PO$_4$ as a base afforded the desired azaindole 11b in a moderate yield (56%, eq 2). Formation of the naphthyridine 13 is attributable to isomerization of the alkyne 10b to the corresponding allene by the action of DBU followed by 6-endo cyclization and elimination of piperidine.

### Table 1. Synthesis of azaindole derivatives 7 using paraformaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu</th>
<th>Base</th>
<th>Additive</th>
<th>R$_2$NH</th>
<th>Time (h)</th>
<th>Yield % (product)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu</td>
<td>–</td>
<td>–</td>
<td>(n-Pr)$_2$NH</td>
<td>10</td>
<td>40 (7a), 20 (8a), 10 (9a)</td>
</tr>
<tr>
<td>2</td>
<td>Cu</td>
<td>K$_3$PO$_4$</td>
<td>–</td>
<td>(n-Pr)$_2$NH</td>
<td>2</td>
<td>decomp.</td>
</tr>
<tr>
<td>3</td>
<td>Cu</td>
<td>Et$_3$N</td>
<td>–</td>
<td>(n-Pr)$_2$NH</td>
<td>10</td>
<td>49 (7a), 17 (8a), 4 (9a)</td>
</tr>
<tr>
<td>4</td>
<td>CuBr</td>
<td>Et$_3$N</td>
<td>–</td>
<td>(n-Pr)$_2$NH</td>
<td>10</td>
<td>42 (7a), 10 (8a), trace (9a)</td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>Et$_3$N</td>
<td>–</td>
<td>(n-Pr)$_2$NH</td>
<td>10</td>
<td>61 (7a), 13 (8a), 5 (9a)</td>
</tr>
<tr>
<td>6</td>
<td>CuCl</td>
<td>Et$_3$N</td>
<td>MS4A</td>
<td>(n-Pr)$_2$NH</td>
<td>2</td>
<td>85 (7a), trace (8a)</td>
</tr>
<tr>
<td>7</td>
<td>CuCl</td>
<td>Et$_3$N</td>
<td>MS4A</td>
<td>piperidine</td>
<td>2</td>
<td>71 (7b)</td>
</tr>
<tr>
<td>8</td>
<td>CuCl</td>
<td>Et$_3$N</td>
<td>MS4A</td>
<td>(i-Pr)$_2$NH</td>
<td>1.5</td>
<td>81 (7c)</td>
</tr>
<tr>
<td>9</td>
<td>CuCl</td>
<td>Et$_3$N</td>
<td>MS4A</td>
<td>Et$_2$NH</td>
<td>2</td>
<td>73 (7d)</td>
</tr>
<tr>
<td>10</td>
<td>CuCl</td>
<td>Et$_3$N</td>
<td>MS4A</td>
<td>diallylamine</td>
<td>1</td>
<td>86 (7e)</td>
</tr>
</tbody>
</table>

$^a$Isolated yields.
We started our synthesis from commercially available 3,4-diaminopyridine 18 (Scheme 6). Treating 18 with bromine in 48\% aqueous HBr afforded the desired bis-brominated product 19. Sonogashira coupling of 19 with an excessive amount of trimethylsilylacetylene failed to introduce two alkynyl groups, instead yielding a mono-alkynylated product 20 in 80\% yield. We expected that the nucleophilicity of the amino group of 20 at the 4 position would be lower than that on the 3 position owing to delocalization of the nitrogen non-bonding electron into the pyridine ring. As hoped, by treating 20 with 2 equiv of MsCl in pyridine in the presence of DMAP, regioselective bis-mesylation of the amino group at the 3 position proceeded readily to produce 21 in 73\% yield. Sonogashira coupling of 21 with trimethylsilylacetylene afforded the desired aminopyridine derivative 22 with two alkynyl groups. Introduction of electron-withdrawing Ms groups would result in a decrease of electron density of the pyridine ring, facilitating a second Sonogashira coupling at the 5 position. Subsequent deprotection of TMS groups and one of the Ms groups produced 23, which underwent regioselective monocyclization in the presence of Et₃N and Cu to yield 24 in 57\% yield in two steps. Then, by use of standard methods for acetylation or mesylation, N-substituted aminoazaindoles 25 and 26 with Ac or Ms group, respectively, were synthesized.
desired cyclization product 27 even with a prolonged reaction time. In our previous study on three-component indole formation, the rate of hydroamination was significantly dependent upon the acidity of the proton on the nitrogen atom.\textsuperscript{18,21} In case of substrate 6a (Scheme 3), a highly electron-withdrawing nitro group \textit{ortho} to the amino group would contribute to an increase in the acidity of the acetamide proton, thereby facilitating hydroamination. The acidity of acetamide proton of 25 (Scheme 7) was considered to be insufficient to promote cyclization.

![Scheme 7. Attempted synthesis of pyrroloazaindole derivative 27](image)

We therefore tested three-component coupling and cyclization with more acidic methanesulfonamide 26 (Table 2). Treating 26 with paraformaldehyde and dipropylamine at room temperature in the presence of 5 mol % of CuI afforded the desired pyrroloazaindole 29 in a low yield (30%) accompanied by generation of a considerable amount of the 2-unsubstituted pyrroloazaindole in the presence of 5 mol % of CuI afforded the desired pyrroloazaindole 29 in a low yield (30%) accompanied by generation of a considerable amount of the 2-unsubstituted pyrroloazaindole 30 (entry 1). Use of a mixed solvent of toluene and dioxane partially suppressed the undesired cyclization at the terminal alkylene before the Mannich-type reaction, resulting in a slightly improved yield of 29 (45%), entry 2). For accelerating the rate of the Mannich-type reaction, a mixture of paraformaldehyde and dipropylamine in toluene was heated at 80 °C for 5 min, then added to the mixture of 26 in dioxane. As hoped, the desired product 29 was isolated in an improved yield (70%) with only a trace amount of the undesired product 30 (entry 3). The pyrroloazaindole 29 is stable in a solid state, whereas it was found to readily undergo a ring cleavage reaction in CDCl\textsubscript{3}. After 24 hours at room temperature, formation of a ring-cleavage product 31 (31/29 = 4:1) was detected by \textsuperscript{1}H NMR analysis (Scheme 8).

![Table 2. Synthesis of pyrroloazaindole derivative 29](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield %</th>
<th>29</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dioxane</td>
<td>30</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>toluene/dioxane (1:1)</td>
<td>45</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>3*</td>
<td>toluene/dioxane (1:1)</td>
<td>70</td>
<td>trace</td>
<td></td>
</tr>
</tbody>
</table>

* Reactions were carried out with (HCHO)\textsubscript{n} (2 equiv) and (n-Pr)\textsubscript{2}NH (1 equiv) using CuI (5 mol %) in toluene at rt. \textsuperscript{*} Isolated yields. \textsuperscript{*} A solution of (HCHO)\textsubscript{n} and (n-Pr)\textsubscript{2}NH in toluene (heated at 80 °C for 5 min) was added to the reaction mixture.

For suppressing this undesired ring-cleavage reaction and undertaking further functionalization of the \textit{N}-protected pyrroloazaindole 29, we tested the deprotection of Ms groups (Scheme 9). To our surprise, treating 29 with Cs\textsubscript{2}CO\textsubscript{3} in MeOH at 70 °C afforded a mono-deprotected ring-cleavage product 32 in 12% yield, together with the major product 33, which was considered to be generated from 32 by its cyclization. A plausible mechanism for the formation of 33 is shown in Scheme 10. First, the carbanion 34 would be formed by deprotonation of the sulfonamide 32 derived from the ring cleavage reaction of 29. The subsequent 6-\textit{exo} cyclization of 34 followed by an isomerization of alkene would afford 33.

![Scheme 8. Ring-cleavage reaction of 29 in CDCl\textsubscript{3}](image)

![Scheme 9. Attempted removal of the Ms groups of 29](image)

![Scheme 10. Plausible mechanism for the formation of 33](image)

Faced with the difficulty of the deprotection of Ms groups from 29, we decided to remove the Ms group of 26 on the pyrrole ring first (Scheme 11). The deprotection of 26 proceeded readily to give 36, which underwent three-component coupling and cyclization with paraformaldehyde and dipropylamine under the condition optimized in Table 2 to furnish the mono-deprotected pyrroloazaindole 37 in a slightly decreased yield (65%). To our delight, fully deprotected pyrroloazaindole 27 could be derived from 37 in 78% yield by treating with Cs\textsubscript{2}CO\textsubscript{3} in MeOH. The azaindoles 37 and 27 can be applied to further functional-group modifications, including \textit{N}-alkylation or \textit{N}-acylation for identification of novel CK2 inhibitors.
4.2. Preparation of 6a

4.2.1. 3-Bromo-5-nitropyridin-4-amine (39). To a stirred mixture of 38 (3.0 g, 21.6 mmol) and NaOAc (2.7 g, 32.4 mmol) in glacial AcOH (72 mL) was added dropwise a mixture of Br2 (3.8 g, 23.8 mmol) in glacial AcOH (24 mL), then the mixture was stirred for 48 h at room temperature. The reaction was quenched with saturated aqueous Na2S2O3 (10 mL), then the solvent was removed under reduced pressure. The resulting yellow solid was collected by filtration and washed with water (50 mL), then dried under vacuum. The crude product was recrystallized from n-hexane–EtOAc (3:1) to give 39 (3.2 g, 67% yield) as yellow crystals.1H and 13C NMR data were in agreement with those previously reported.28

4.2.2. N-(3-Bromo-5-nitropyridin-4-yl)acetamide (40). To a stirred mixture of 39 (2.0 g, 9.2 mmol) and DMAP (113 mg, 0.92 mmol) in DMF (10 mL) were added pyridine (3.7 mL, 46 mmol) and acetic anhydride (4.3 mL, 46 mmol), and the mixture was stirred for 2 h at 100 °C. After being cooled to room temperature, the resulting black mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with n-hexane–EtOAc (2:1), then recrystallized from n-hexane–EtOAc (3:1) to give 40 (1.1 g, 46% yield) as colorless crystals: Rr = 0.50 (silica gel, n-hexane/EtOAc = 1:1); mp 197 °C; IR (neat) cm−1 1681 (C=O), 1487 (NO2);1H NMR (500 MHz, DMSO-d6) δ: 2.15 (3H, s), 8.92 (1H, s), 9.01 (1H, s), 10.71 (1H, s); 13C NMR (125 MHz, DMSO-d6) δ: 21.8 (s), 71.8 (s), 141.2 (s), 144.7 (d), 155.9 (d), 168.8 (s). Anal. Calcd for C13H12N3O3: C, 52.65; H, 3.27; N, 20.43; O, 23.59. Found: C, 52.65; H, 3.27; N, 20.43.

4.2.3. N-[3-Nitro-5-[(trimethylsilyl)ethylnyl]pyridin-4-yl]acetamide (41). A mixture of 40 (500 mg, 1.9 mmol), trimethylsilacyclene (0.4 mL, 2.8 mmol), Cul (19 mg, 0.1 mmol), PdCl2(PPh3)2 (70 mg, 0.1 mmol), and Et3N (1 mL) in THF (10 mL) was stirred at 60 °C for 2 h under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with n-hexane–EtOAc (5:1) to give 41 (348 mg, 65% yield) as brown crystals: Rr = 0.65 (silica gel, n-hexane/EtOAc = 1:1); mp 135 °C; IR (neat) cm−1 1589 (C=O), 1492 (NO2);1H NMR (500 MHz, CDCl3) δ: 3.8 (9H, s), 2.37 (7H, s), 8.21 (1H, br s), 8.76 (1H, s), 8.97 (1H, s);13C NMR (125 MHz, CDCl3) δ: 0.0 (3C, q), 24.2 (q), 95.7 (s), 108.8 (s), 115.0 (s), 138.6 (s), 145.7 (d), 156.2 (d), 167.7 (s). Anal. Calcd for C17H16N3O3Si: C, 51.97; H, 5.45; N, 15.15. Found: C, 51.77; H, 5.48; N, 15.14.

4.2.4. N-(3-Ethynyl-5-nitropyridin-4-yl)acetamide (6a). To a stirred mixture of 41 (300 mg, 1.1 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol) under argon, and the mixture was stirred for 10 min at 0 °C. The mixture was quenched with saturated aqueous NH4Cl (1 mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried over MgSO4, and evaporated. The residue was purified by column chromatography over silica gel with n-hexane–EtOAc (2:1), then recrystallized from n-hexane–EtOAc (3:1) to give 6a (158 mg, 71% yield) as brown crystals: Rr = 0.25 (silica gel, n-hexane/EtOAc = 2:1); mp 90 °C (decomp.); IR (neat) cm−1 3271 (C=N), 1694 (C=O), 1448 (NO2).1H NMR (500 MHz, CDCl3) δ: 2.14 (3H, s), 4.94 (1H, s), 8.94 (1H, s), 9.01 (1H, s), 10.71 (1H, s); 13C NMR (125 MHz, CDCl3) δ: 22.8 (q), 75.5 (s), 91.1 (d), 115.0 (s), 138.8 (s), 140.7 (s), 145.3 (d), 156.9 (d), 168.9 (s). Anal. Calcd for C17H14N4O2Si: C, 52.69; H, 3.44; N, 20.48; O, 23.39. Found: C, 52.65; H, 3.27; N, 20.43; O, 23.59.

4.3. Copper-catalyzed three-component coupling and cyclization of 6a with various aldehydes and secondary amines

4.3.1. General procedure for the synthesis of 7 using paraformaldehyde: synthesis of N-[(7-nitro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]-N-propylpropan-1-amine (7a) (Table 1, entry 6). To a stirred mixture of 6a (30 mg, 0.15 mmol), paraformaldehyde (9 mg, 0.29 mmol), CuCl (1.5 mg, 0.015...
mmol), Et3N (0.04 mL, 0.29 mmol) and MS4A (73 mg in dioxane (1.5 mL) was added dipropylamine (0.02 mL, 0.15 mmol), and the mixture was stirred for 2.5 h at 80 °C under argon. After being cooled to room temperature, the mixture was washed through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (5:1) to give 7a (34 mg, 85% yield) as a yellow solid: Rf = 0.60 (alumina, n-hexane/EtOAc = 3:1); mp 123 °C; IR (neat) cm−1 1522 (NO2); 1H NMR (500 MHz, CDCl3) δ: 3.16 (4H, d, J = 6.3 Hz), 3.83 (2H, s), 5.21-5.26 (4H, m), 5.85-5.94 (2H, m), 6.58 (1H, s), 9.00 (1H, s), 9.17 (1H, s), 10.15 (1H, br s)); 13C NMR (125 MHz, CDCl3) δ: 49.9 (t), 56.7 (2C, t), 101.1 (d), 118.5 (2C, t), 128.5 (s), 130.2 (s), 132.7 (s), 134.7 (2C, d), 138.0 (d), 141.5 (s), 147.6 (d); HRMS (FAB) calcd for C12H17N4O2 [M+H]+: 273.1352, found: 273.1348.

4.6. N-[3-f3-[Dipropylamino]prop-1-yl]yl-5-nitropyridine-4-ylacetamide (8a) and N-[N-(7-nitro-1H-pyrrolo[3,2-c]pyridine-2,3-diyli)bismethylene]bis(N-propylprop-1-amine) (9a) (Table 1, entry 1). To a stirred mixture of 6a (50 mg, 0.24 mmol), paraformaldehyde (15 mg, 0.48 mmol) and CuI (4.6 mg, 0.024 mmol) in dioxane (2.0 mL) was added dipropylamine (0.033 mL, 0.24 mmol), then the mixture was stirred for 10 h at 80 °C under argon. After being cooled to room temperature, the mixture was washed through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (10:1) to give 7a (26 mg, 40% yield), 8a (15 mg, 20% yield) and 9a (9 mg, 10% yield).

Compound 8a: light yellow solid; Rf = 0.25 (alumina, n-hexane/EtOAc = 3:1); mp 151 °C; IR (neat) cm−1 2217 (C≡C), 1683 (C=O), 1496 (NO2); 1H NMR (500 MHz, CDCl3) δ: 0.94 (6H, t, J = 7.2 Hz), 1.50-1.57 (4H, m), 2.27 (2H, s), 2.50 (4H, t, J = 7.4 Hz), 3.72 (2H, s), 8.24 (1H, br s), 8.76 (1H, s), 8.97 (1H, s); 13C NMR (125 MHz, CDCl3) δ: 11.8 (2C, q), 20.7 (2C, t), 23.9 (q), 42.0 (t), 56.0 (2C, t), 76.2 (s), 97.6 (s), 114.9 (s), 137.8 (s), 139.2 (s), 144.9 (d), 151.6 (d), 167.4 (s); HRMS (FAB) calcd for C21H36N5O2 [M+H]+: 319.1770, found: 319.1771.

Compound 9a: yellow oil; Rf = 0.75 (alumina, n-hexane/EtOAc = 3:1); IR (neat) cm−1 1520 (NO2); 1H NMR (500 MHz, CDCl3) δ: 0.83 (6H, t, J = 7.4 Hz), 0.91 (6H, t, J = 7.4 Hz), 1.46-1.55 (8H, m), 2.35 (4H, t, J = 7.4 Hz), 2.45 (4H, t, J = 7.4 Hz), 3.68 (2H, s), 3.77 (2H, s), 9.16 (1H, s), 9.24 (1H, s), 10.09 (1H, br s); 13C NMR (125 MHz, CDCl3) δ: 11.8 (2C, q), 12.0 (2C, q), 20.18 (2C, t), 20.20 (2C, t), 48.5 (t), 49.9 (t), 55.9 (2C, t), 56.4 (2C, t), 112.0 (s), 129.3 (s), 130.0 (s), 132.0 (s), 137.9 (d), 139.3 (s), 147.8 (d); HRMS (FAB) calcd for C24H34N6O2 [M+H]+: 390.2869, found: 390.2863.

4.7. 7-Nitro-2-[1-(piperidine-1-yl)butyl]-1H-pyrrolo[3,2-c]pyridine (11a). A mixture of 6a (60 mg, 0.29 mmol), butanal (0.055 mL, 0.58 mmol), piperidine (0.035 mL, 0.35 mmol) and CuCl (3 mg, 0.03 mmol) in dioxane (2 mL) was stirred at 80 °C for 15 min under argon. After Mannich-type three-component coupling was completed (monitored by TLC), DBU (0.09 mL, 0.8 mmol) was added. The resulting mixture was stirred for additional 30 min at 80 °C under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (4:1) to give 11a (58 mg, 68% yield) as an orange oil; Rf = 0.75 (alumina, n-hexane/EtOAc = 3:2); IR (neat) cm−1 1523 (NO2); 1H NMR (500 MHz, CDCl3) δ: 0.94 (3H, t, J = 7.4 Hz), 1.28-1.44 (4H, m), 1.54-1.59 (4H, m), 1.70-1.78 (1H, m), 1.90-1.97 (1H, m), 2.42-2.49 (4H, m), 3.66 (2H, d, J = 8.9, 4.9 Hz), 5.64 (1H, s), 8.99 (1H, s), 9.15 (1H, s), 10.15 (1H, br s); 13C NMR (125 MHz, CDCl3) δ: 14.1 (q), 20.4 (t), 24.5 (t), 26.3 (2C, t), 31.9 (t), 51.0 (2C, t), 63.1 (d), 100.8 (d), 128.4 (s), 130.2 (s), 132.4 (s), 137.9 (d), 144.9 (s), 147.5 (d); HRMS (FAB) calcd for C18H21N4O2 [M+H]+: 303.1821, found: 303.1818.
4.3.8. 7-Nitro-2-[(phenylpiperidin-1-yl)methyl]-1H-pyrrolo[3,2-c]pyridine (11b). A mixture of 6a (50 mg, 0.24 mmol), benzaldehyde (0.05 mL, 0.49 mmol), piperidine (0.025 mL, 0.24 mmol) and CuCl (2.4 mg, 0.024 mmol) in dioxane (2 mL) was stirred at 80 °C for 30 min under argon. After being cooled to room temperature, solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (3:1) to give a mixture of 10b (54 mg, 59% yield) and 12 (7 mg, 18% yield). To this mixture were added CuCl (1.5 mg, 0.015 mmol), K₂PO₄ (62 mg, 0.29 mmol) and dioxane (2 mL), then the mixture was stirred at 80 °C for 4.5 h under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with n-hexane–EtOAc (5:1) to give 11b (28 mg, 56% yield from 10b) as a brown oil; Rᵣ = 0.80 (alumina, n-hexane/EtOAc = 1:1); IR (neat) cm⁻¹ 3522, 3477, 3385 (NH × 2), 2164 (C=O), 1366, 1156 (SO₂); 1H NMR (500 MHz, CDCl₃) δ: 1.43-1.45 (2H, m), 1.63-1.64 (4H, m), 2.36-2.42 (4H, m), 4.77 (1H, s), 6.51 (1H, s), 7.33-7.40 (5H, m), 8.95 (1H, s), 9.17 (1H, s), 10.26 (1H, br s); 13C NMR (125 MHz, CDCl₃) δ: 24.3 (t), 26.2 (2C, t), 52.1 (2C, t), 69.2 (d), 101.5 (d), 128.2 (d), 128.5 (s), 128.6 (2C, d), 128.8 (2C, d), 130.3 (s), 132.7 (s), 136.9 (s), 138.1 (d), 144.4 (s), 147.7 (d); HRMS (FAB) calcd for C₁₀H₁₀N₃O₂ [M+H⁺]: 307.0775, found: 307.0775.

4.3.9. 8-Nitro-2-phenyl-1,6-naphthyridine (13). By a procedure identical with that described for the preparation of 11b, 6a (50 mg, 0.24 mmol) was converted into 10b (54 mg, 59% mixed with 12 (7 mg, 18% yield) by the reaction with benzaldehyde (0.05 mL, 0.49 mmol), CuCl (2.4 mg, 0.024 mmol) and piperidine (0.025 mL, 0.24 mmol). To this mixture were added CuCl (1.5 mg, 0.015 mmol), DBU (0.043 mL, 0.29 mmol) and dioxane (2 mL), then the mixture was stirred at 80 °C for 30 min under argon. After being cooled to room temperature, solvent was removed and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (5:1) to give 13 (21 mg, 60% yield from 10b) as a brown solid; Rᵣ = 0.60 (alumina, n-hexane/EtOAc = 1:1); mp 185 °C (decomp.); IR (neat) cm⁻¹ 1522 (3H, m), 8.18 (1H, d, J = 8.7 Hz), 9.13 (1H, s), 9.39 (1H, s); 13C NMR (125 MHz, CDCl₃) δ: 121.4 (d), 123.2 (s), 128.3 (2C, d), 129.2 (2C, d), 131.5 (d), 136.3 (d), 136.7 (s), 138.5 (s), 141.7 (d), 142.2 (s), 156.5 (d), 163.2 (s); HRMS (FAB) calcd for C₁₀H₈BrN₂O₂ [M⁺H⁺]: 252.0772, found: 252.0772.

4.3.10. 2-[(Dipropylamino)methyl]-1H-pyrrolo[3,2-c]pyridin-7-amine (14). A mixture of 7a (50 mg, 0.18 mmol) and 10% Pd/C (5 mg) in MeOH (2 mL) was stirred at room temperature for 1 h under H₂ atmosphere. Then, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with CHCl₃–MeOH (30:1) to give 14 (38 mg, 85% yield) as a brown oil; Rᵣ = 0.50 (alumina, CHCl₃/MeOH = 10:1); IR (neat) cm⁻¹ 3400, 3190 (NH × 2); 1H NMR (500 MHz, DMSO-d₆) δ: 0.83 (6H, t, J = 7.2 Hz), 1.41-1.49 (4H, m), 2.38 (4H, t, J = 7.4 Hz), 3.67 (2H, s), 5.16 (2H, br s), 6.26 (1H, s), 7.51 (1H, s), 8.04 (1H, s), 10.71 (1H, s); 13C NMR (125 MHz, DMSO-d₆) δ: 11.8 (2C, q), 19.5 (2C), 51.3 (s), 55.4 (2C, t), 99.4 (d), 124.6 (d), 125.2 (s), 128.9 (s), 129.8 (s), 131.4 (d), 137.5 (s); HRMS (FAB) calcd for C₁₀H₈N₂ [M⁺H⁺]: 174.1923, found: 174.1922.

4.4. Synthesis of pyrrole-fused azaindoles

The compound 19 was prepared from commercially available 3,4-diaminopyridine 18 according to a reported literature.27
4.4.2. N-{6-[3-(Dipropylamino)-prop-1-ynyl]-1H-pyrrolo[3,2-b]-pyridin-7-yl}acetamide (28). To a stirred mixture of 25 (24 mg, 0.12 mmol), paraformaldehyde (8 mg, 0.24 mmol), CuCl (1.3 mg, 0.012 mmol), Et3N (0.04 mL, 0.24 mmol) and MS4A (70 mg) in dioxane (1.5 mL) was added dipropylamine (0.02 mL, 0.12 mmol), and the mixture was stirred for 5 h at 80 °C under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (4:1) to give 28 (16 mg, 42% yield) as a yellow solid: Rf = 0.50 (alumina, n-hexane–EtOAc = 2/1); mp 168 °C; IR (neat) cm–1 3223 (C–H); 1H NMR (500 MHz, CDCl3) δ: 2.4 (4H, br s), 8.26 (1H, s), 8.48 (1H, s), 10.70 (1H, br s); 13C NMR (125 MHz, CDCl3) δ: 2.31 (3H, s), 3.57 (1H, s), 6.10 (2H, s), 6.82 (1H, d, J = 4.6 Hz), 7.66 (1H, d, J = 4.6 Hz), 8.41 (1H, s); HRMS (FAB) calcd for C10H10N3O2S [M+H]+: 236.0500, found: 236.0500.

4.4.9. N-{[1,8-Bis(methylsulfonyl)]-1,8-dihydrodipyrrrolo[3,2-b:2',3'-d]pyridin-7-yl}-methyl]-N-propylpropan-1-amine (29) (Table 2, entry 3). To a stirred mixture of 26 (100 mg, 0.32 mmol) and Cu (3 mg, 0.016 mmol) in dioxane (1 mL) was added a preheated solution (80 °C for 5 min) of paraformaldehyde (19 mg, 0.64 mmol) and dipropylamine (0.044 mL, 0.32 mmol) in toluene (1 mL), and then the mixture was stirred at room temperature for 30 min under argon. Solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (2:1) to give 29 (95 mg, 70% yield) as a white solid: Rf = 0.70 (alumina, n-hexane–EtOAc = 1/1); mp 102 °C; IR (neat) cm–1 1361, 1296, 1116, 1146 (SO2 × 2); 1H NMR (500 MHz, CDCl3) δ: 0.91 (6H, t, J = 7.4 Hz), 1.48–1.56 (4H, m), 2.24–2.48 (4H, m), 3.32 (3H, s), 3.44 (1H, dd, J = 15.5, 6.9 Hz), 3.47 (1H, dd, J = 15.5, 6.9 Hz), 3.82 (3H, s), 5.86 (1H, dd, J = 6.9, 6.9 Hz), 6.76 (1H, d, J = 4.0 Hz), 7.81 (1H, d, J = 4.0 Hz), 8.50 (1H, s); 13C NMR (125 MHz, CDCl3) δ: 11.8 (2C, q), 20.3 (2C, t), 40.3 (q), 48.3 (t), 56.1 (2C, t), 107.5 (d), 111.8 (d), 120.3 (s), 131.3 (s), 135.4 (s), 142.8 (d), 145.6 (s), 151.2 (d), 152.0 (s); HRMS (FAB) calcd for C16H15N3O2S [M+H]+: 427.1474, found: 427.1466.

4.4.10. 1,8-Bis(methylsulfonyl)-1,8-dihydrodipyrrrolo[3,2-b:2',3'-dipyridine (30). To a stirred mixture of 26 (50 mg, 0.16 mmol) and Cu (1.5 mg, 0.008 mmol) in dioxane (1 mL) were added paraformaldehyde (10 mg, 0.32 mmol) and dipropylamine (0.022 mL, 0.16 mmol), then the mixture was stirred at room temperature for 30 min under argon. The solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with n-hexane–EtOAc (3:1) to give 30 (29 mg, 30% yield) and 30 (15 mg, 29% yield).

Compound 30: white solid; Rf = 0.45 (alumina, n-hexane–EtOAc = 1/1); mp 170 °C; IR (neat) cm–1 1363, 1320, 1165, 1108 (SO2 × 2); 1H NMR (500 MHz, CDCl3) δ: 3.30 (3H, s), 3.82 (3H, s), 5.11 (1H, d, J = 3.4 Hz), 5.34 (1H, d, J = 3.4 Hz), 6.77 (1H, d, J = 3.9 Hz), 7.83 (1H, d, J = 3.9 Hz), 8.57 (1H, s); 13C NMR (125 MHz, CDCl3) δ: 49.5 (q), 53.8 (q), 105.7 (s), 117.2 (d), 119.4 (s), 129.8 (s), 141.1 (d), 145.2 (s), 152.7 (d), 161.1 (d), 161.3 (s); HRMS (FAB) calcd for C16H15N3O2S [M+H]+: 427.1474, found: 427.1466.

4.4.11. N-{[6-[3-(Dipropylamino)-prop-1-ynyl]-1H-pyrrolo[3,2-b]-pyridin-7-yl]methyl}-N-propylpropan-1-amine (31). A solution of 29 (20 mg, 0.05 mmol) in CDCl3 (0.5 mL) was placed in a NMR tube. After 24 h at room temperature, 1H NMR analysis showed that 29 was converted to 31 with a ratio of 4:1.
The mixture was purified by column chromatography over silica gel with CHCl₃–MeOH (9:1 to give 31 (13 mg, 65% yield) as an orange solid; R₉ = 0.50 (silica gel, CHCl₃/MeOH = 9/1); IR (neat) cm⁻¹ 3228 (C=O), 1349, 1316, 1158, 1137 (SO₂ × 2); ¹H NMR (500 MHz, CDCl₃) δ: 0.94 (6H, t, J = 7.2 Hz), 1.52-1.57 (4H, m, 2.94 (4H, m, 2.9 Hz), 4.13 (1H, s, 6.44 (1H, m, 4.4 Hz), 7.67 (1H, dd, J = 3.0, 3.0 Hz), 8.22 (1H, ss), 11.16 (1H, ss), 13.15 (1H, br s). ¹³C NMR (125 MHz, CDCl₃-d₆) δ: 42.1 (q), 79.6 (s), 83.7 (d), 96.7 (s), 103.1 (s), 108.4 (d), 124.3 (s), 127.1 (d), 130.7 (s), 143.4 (d). HRMS (FAB) calec for C₁₇H₂₅N₄O₂S [M+H⁺]: 349.1698, found: 349.1696.

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References and notes


26. Deprotection of the acetyl group is considered to proceed readily via hydrolysis of the amide bond during the reaction and/or work-up. For examples of the deprotection of trifluoroacetyl group during indole formation, see: Lu, B. Z.; Zhao, W.; Wei, H.; Dufour, M.; Farina, V.; Senanayake, C. H. Org. Lett. 2006, 8, 3271–3274. See also, ref 9.