Azine and Diazine Functionalization Using 2,2,6,6-Tetramethylpiperidino-Based Lithium–Metal Combinations: Application to the Synthesis of 5,9-Disubstituted Pyrido[3’,2’:4,5]pyrrolo[1,2-c]pyrimidines

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Azine and Diazine Functionalization Using 2,2,6,6-Tetramethylpiperidino-Based Lithium–Metal Combinations: Application to the Synthesis of 5,9-Disubstituted Pyrido[3′,2′:4,5]pyrrolo[1,2-c]pyrimidines

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Abstract The synthesis of triaryl methanols was investigated by reacting different 4-metalated 2-substituted pyrimidines with diaryl ketones, the latter being generated by deprotocupration–aroylation of azine and diazine substrates. Cyclization of the triaryl methanols thus obtained afforded pyrido[3′,2′:4,5]pyrrolo[1,2-c]pyrimidines, which were evaluated for kinase inhibition and antiproliferative activities in melanoma cells.

Key words diaryl ketone, pyrimidine, deprotometalation, mixed-metal amide, variolin analogue

Variolins are a family of marine alkaloids isolated from the Antarctic sponge Kirkpatrickia varialosa. Among them, variolin B is a tricyclic system bearing a substituent at the 5-position endowed with biological properties such as antitumor and antiviral. Several total syntheses of variolin B and analogues have been reported. In the convergent synthesis of Morris, the key step involves the tandem deoxygenation–cyclization of a triaryl methanol, the latter being for example obtained by reaction of 2-chloro-3-methoxypyridine on a symmetrical ketone (Scheme 1).

Because of our interest in the synthesis of diaryl ketones by deprotocupration–aroylation, we decided to evaluate the reactivity of these ketones toward different 4-metalated 2-substituted pyrimidines in order to reach different triaryl methanols. Thus, the required diaryl ketones were prepared from azines or diazines as reported previously. The latter were deprotocuprated at room temperature in tetrahydrofuran (THF) containing N,N,N′,N′-tetramethylethylenediamine (TMEDA) by using (TMP)₂CuLiLiCl (TMP = 2,2,6,6-tet-
ramethylpiperidino), prepared in situ from CuCl and LiTMP (2 equiv). Trapping with aryl chlorides after two hours furnished the compounds 1a–i (Scheme 2).

We next considered the formation of 4-metalated 2-chloropyrimidine from 2 and its trapping. The pyrimidine 2 being prone to nucleophilic attacks, we first tried to use the base prepared in situ by mixing ZnCl₂·TMEDA and LiTMP in a 1:3 ratio, and supposed to be a 1:1 LiTMP₂[ZnCl₂(TMEDA)]₂–Zn(TMEDA)₂ mixture. It proved not appropriate, with the iodide 4a isolated in a low 18% yield when the deprotonation step was performed at 0 °C and only degradation noticed at higher temperatures. TMPMgCl·LiCl being a suitable base for 2 in THF at –60 °C, as evidenced by subsequent iodolysis after two hours, we thus employed it in order to attempt the interception of the deprotonated species with the ketone 1a. The expected triaryl methanol 4b was obtained in a moderate 33% yield by carrying out the reaction at –60 °C, but its formation could be improved with a deprotonation step at –40 °C (Scheme 3).

4-Metalated derivatives of 2-(methylthio)pyrimidine (3) could be formed at room temperature in THF by using either the previous lithium–zinc base or the corresponding lithium–cadmium base, prepared in situ by mixing CdCl₂·TMEDA (0.5 equiv) and LiTMP (1.5 equiv). This was evidenced by iodolysis to afford 5a in correct yields. When TMPMgCl·LiCl was employed at –60 °C, the alcohol 5b resulting from a quenching with the ketone 1a was obtained in a moderate 21% yield (Scheme 4).

To reach the triaryl methanols, it also proved possible to involve the iodide 5a in a butyllithium-mediated halogen–metal exchange reaction in the presence of the ketone 1a or 1b. Performing this reaction in THF at –95 °C, as previously documented by Morris, led to the alcohol 5b or 6b in 72% or 45% yield, respectively. Replacing methanol quenching with acetyl chloride afforded the corresponding acetate 5b'. Finally, treating both 5b and 5b' with triethylsilane and trifluoroacetic acid at 100 °C in 1,2-dichloroethane furnished the phenyl-substituted tricycle 7b in 45% yield (Scheme 5). Because no improvement was here noted by using the acetate 5b' as intermediate, we kept the sequence involving triaryl methanols for the rest of the study.

In order to prepare analogues of 9-(methylthio)-5-phenylpyrido[3′,2′;4,5]pyrrolo[1,2-c]pyrimidine (7b), we aimed at synthesizing various triaryl methanols (Table 1). When 2-chloro-4-iodopyrimidine (4a) was involved instead of 5a in the reaction with 1a, a lower 24% yield was noticed (Table 1, entries 1 and 2). With the other ary[2-chloro-3-pyridyl]methanones 1c–e, the expected alcohols were isolated in yields ranging from 52–70% (Table 1, entries 3–5). The position of chlorine on the (2-chloro-3-pyridyl)(chloro-3-pyridyl)methanone is an important parameter for the success of the reaction. Indeed, whereas a good 75% yield was registered by using 1f (compound 5f, Table 1, entry 6), a complex mixture without the expected derivative togeth-
er with starting material was obtained from 1g (Table 1, entry 7). With the ketones 1h and 1i bearing a pyrimidyl group, things become difficult, probably in relation with ring sensitivity to nucleophilic attacks; as a consequence, the alcohol 5i was the only to be formed, in a very low 8% yield (Table 1, entries 8 and 9).

Table 1 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate X</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5a SMe 1d</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5a SMe 1e</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5a SMe 1f</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5a SMe 1g</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5a SMe 1h</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5a SMe 1i</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

In order to progress toward the corresponding 5-aryl tricycles, the triaryl methanols were submitted to the action of triethylsilane and trifluoroacetic acid as before (Table 2). Under these conditions, the targets 7b–f were generated in moderate yields (Table 2, entries 2–6). No cyclization was noticed from the dichloride 4b (Table 2, entry 1). Similarly, cyclization of the dichloride 6b did not take place under the conditions used (Table 2, entry 7). In both cases, starting material was recovered.
Variolin B was characterized as a potent inhibitor of cyclin-dependent kinases (CDK), key actors involved notably in the regulation of the cell-division cycle, programmed cell-death by apoptosis, transcription as well as differentiation. This chemical scaffold was consequently used to design new inhibitors of CDK. In this study we thus tested the new derivatives on a panel of nine protein kinases including CDK5: HsAurora B, HsCDK5/p25, HsRIPK3 (receptor interacting protein kinase), HsHaspin; porcine (Sus scrofa) SsGSK-3 (glycogen synthase kinase-3) and SsCK1 (casein kinase 1); kinases from the protozoan parasites, Leishmania major LmCK1, Plasmodium falciparum PfGSK-3, and from Leishmania donovani LdTLK (tousled-like kinase). These kinases were not significantly affected by the tested chemical compounds (5b–e and 7c–f) with none of the molecules causing more than 50% inhibition of enzymatic activity at 10⁻⁵ M.

The antiproliferative activity of the 5,9-disubstituted pyrido[3′,2′:4,5]pyrrolo[1,2-c]pyrimidines 5b–e and 7c–f was studied in the A2058 (ATCC® CRL-11147) melanoma cell line (Figure 1). A2058 are highly invasive human epithelial adherent melanoma cells, derived from lymph nodes metastatic cells obtained from a 43 years male patient. They are tumorigenic at 100% frequency in nude mice and considered as very resistant to anticancer drugs.

The compounds 5 exerted low antiproliferative activity in A2058 melanoma cells, with 0–13% growth inhibition in cells treated for 72 h at 10⁻⁵ M. In contrast, the compounds 7 exhibited 23–44% growth inhibition and were considered as moderately antiproliferative. This activity was not correlated to CDK inhibition, as all molecules were inactive at 10⁻⁵ M in the CDK inhibition assay. Because of the presence of the sp³ carbon, the compounds 5 are not planar in contrast to the compounds 7. This observation indicates that the planar structure improves the antiproliferative activity and suggests that the cytotoxicity of these new compounds may be related to a DNA intercalating activity, as previously reported with variolin analogues. The nature of the ring...
connected to the tricycle also plays an important role, as the absence of cycle leads to a complete loss of activity, as observed with variolin D.\(^{1c}\) Moreover, the presence of ring nitrogens or/and amino function is also critical for CDK inhibition.\(^{2a}\)

As a conclusion, 2-substituted pyrimidines could be functionalized at their 4-position by using a lithium–metal TMP-based deprotonating agent.\(^{12–14}\) The triaryl methanols obtained either after subsequent quenching, or through iodine–lithium exchange with in situ ketone trap, were cyclized to afford new pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidines.

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**Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560496.

**References and Notes**


(12) 2-Chloro-α-(2-chloro-3-pyridyl)-α-phenyl-4-pyrimidine-methanol (4b)

i-PrMgCl-LiCl (about 1.3 M THF solution, 1.2 mmol) was stirred with 2,2,6,6-tetramethylpiperidine (0.21 mL, 1.2 mmol) at r.t. for 48 h. The resulting solution was cooled to −60 °C before introduction of a cooled solution of 2-chloropyrimidine (2, 0.11 g, 1.0 mmol) in THF (2 mL). After 2 h at −40 °C, a solution of the ketone 1a (0.26 g, 1.2 mmol) in THF (4 mL) was added at −60 °C. The mixture was stirred overnight at r.t. before addition of H₂O (0.5 mL) and dilution with EtOAc (20 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification was performed by chromatography on silica gel (eluent: heptane–EtOAc, 7:3) to afford 4b in 51% yield as a yellow powder; mp 90 °C. ¹H NMR (300 MHz, CDCl₃): δ = 4.97 (s, 1 H), 7.18 (dd, 1 H, J = 7.8, 4.7 Hz), 7.33 (dd, 1 H, J = 7.8, 1.9 Hz), 7.36 (d, 1 H, J = 5.2 Hz), 8.37 (dd, 1 H, J = 4.7, 1.9 Hz), 7.35–7.45 (m, 5 H), 8.60 (d, 1 H, J = 5.2 Hz) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 80.5 (C), 117.6 (CH), 122.3 (CH), 127.5 (2 CH), 128.7 (CH), 128.8 (2 CH), 138.2 (C), 139.9 (CH), 140.7 (C), 149.4 (CH), 150.8 (C), 160.1 (CH), 161.0 (C), 175.0 (C) ppm. ESI-HRMS: m/z calc for C₁₇H₁₄Cl₂N₂O [M + Na⁺]: 354.0177; found: 354.0178.

(13) 4-Iodo-2-(methylthio)pyrimidine (5a)

To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.50 mL, 3.0 mmol) in THF (6 mL) were successively added BuLi (about 1.6 M hexanes solution, 3.0 mmol) and, 5 min later, ZnCl₂-TMEDA (0.26 g, 1.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of 2-(methylthio)pyrimidine (3, 0.25 g, 2.0 mmol). After 2 h at this temperature, a solution of Li₂O (0.76 g, 3.0 mmol) in THF (10 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated...
solution of Na₂S₂O₃ (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification was performed by chromatography on silica gel (eluent: heptane–EtOAc, 95:5) to afford 5a in 77% yield as a beige powder; mp 52 °C (ref. 14: 52–53 °C). ¹H NMR (300 MHz, CDCl₃): δ = 2.54 (s, 3 H), 7.40 (d, 1 H, J = 5.1 Hz), 8.00 (d, 1 H, J = 5.1 Hz) ppm.