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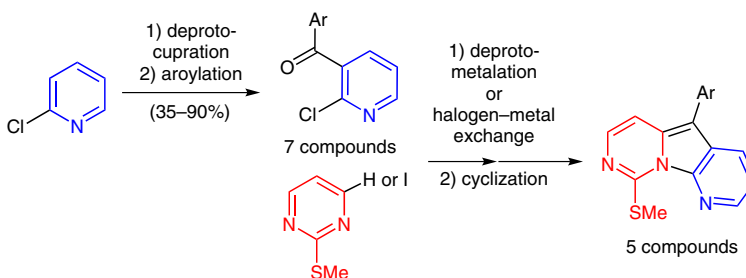
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# Azine and Diazine Functionalization Using 2,2,6,6-Tetramethylpiperidino-Based Lithium–Metal Combinations: Application to the Synthesis of 5,9-Disubstituted Pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidines

Nada Marquise<sup>a</sup>  
 Tan Tai Nguyen<sup>a</sup>  
 Floris Chevallier<sup>a</sup>  
 Laurent Picot<sup>b</sup>  
 Valérie Thiéry<sup>\*b</sup>  
 Olivier Lozach<sup>c</sup>  
 Stéphane Bach<sup>\*c</sup>  
 Sandrine Ruchaud<sup>c</sup>  
 Florence Mongin<sup>\*a</sup>



<sup>a</sup> Equipe Chimie et Photonique Moléculaires, Institut des Sciences Chimiques de Rennes, UMR 6226, CNRS-Université de Rennes 1, Bâtiment 10A, Case 1003, Campus de Beaulieu, 35042 Rennes, France

florence.mongin@univ-rennes1.fr

<sup>b</sup> Laboratoire Littoral Environnement et Sociétés, UMRI CNRS 7266, Université de La Rochelle, 17042 La Rochelle, France

valerie.thiery@univ-lr.fr

<sup>c</sup> USR 3151, CNRS-Université Pierre et Marie Curie, Kinase Inhibitor Specialized Screening Facility, KISSf, Station Biologique, 29680 Roscoff, France

bach@sb-roscoff.fr

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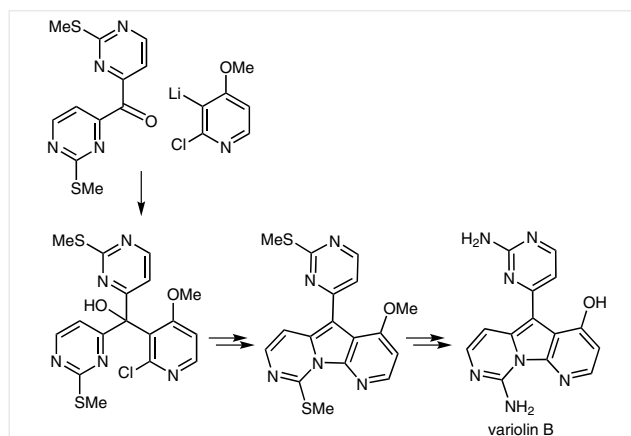
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**Abstract** The synthesis of triaryl methanols was investigated by reacting different 4-metalated 2-substituted pyrimidines with diaryl ketones, the latter being generated by deprotocupration–arylation of azine and diazine substrates. Cyclization 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

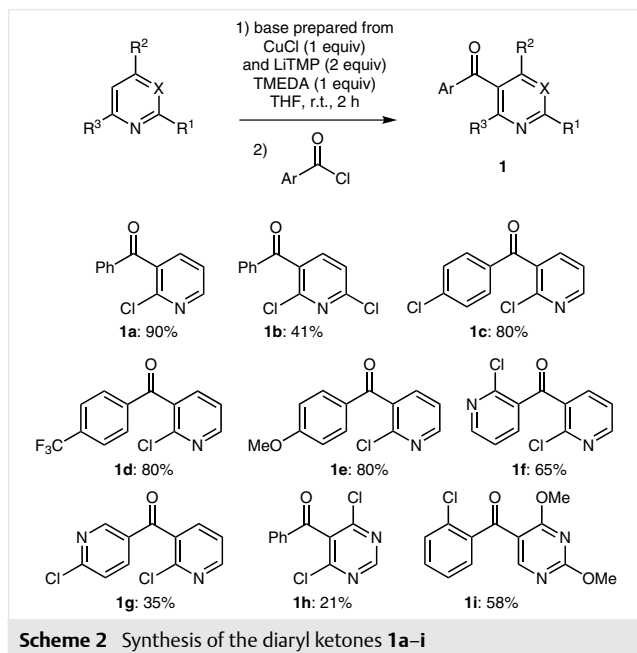
Variolins are a family of marine alkaloids isolated from the Antarctic sponge *Kirkpatrickia variolosa*.<sup>1</sup> Among them, variolin B is a tricyclic system bearing a substituent at the 5-position endowed with biological properties such as anti-tumor and antiviral.<sup>1a,2</sup> Several total syntheses of variolin B and analogues have been reported.<sup>2b,3</sup> In the convergent synthesis of Morris,<sup>3b,3h,4</sup> the key step involves the tandem deoxygenation–cyclization of a triaryl methanol, the latter being for example obtained by reaction of 2-chloro-3-lithio-4-methoxy-pyridine on a symmetrical ketone (Scheme 1).



**Scheme 1** Morris synthesis of variolin B

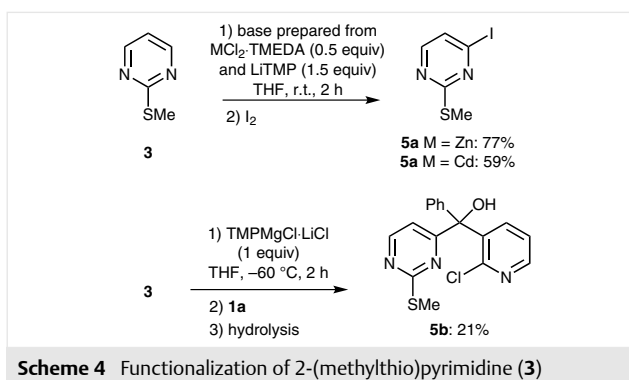
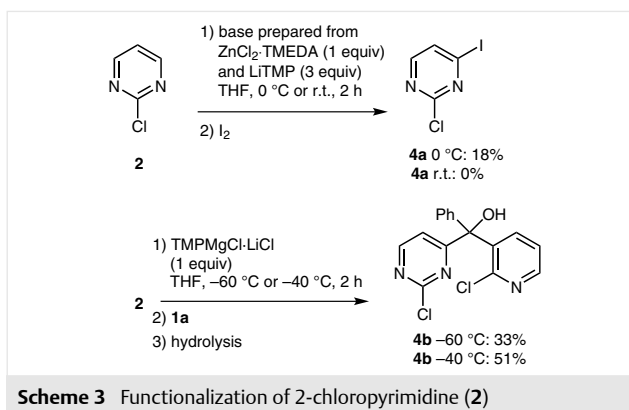
Because of our interest in the synthesis of diaryl ketones by deprotocupration–arylation,<sup>5</sup> we decided to evaluate the reactivity of these ketones toward different 4-metalated 2-substituted pyrimidines in order to reach different triaryl methanols. Thus, the required diaryl ketones were prepared from azines or diazines as reported previously.<sup>5</sup> The latter were deprotocuprated at room temperature in tetrahydrofuran (THF) containing *N,N,N',N'*-tetramethylethylenediamine (TMEDA) by using (TMP)<sub>2</sub>CuLi·LiCl (TMP = 2,2,6,6-tet-

ramethylpiperidino), prepared in situ from CuCl and LiTMP (2 equiv). Trapping with aroyl chlorides after two hours furnished the compounds **1a–i** (Scheme 2).



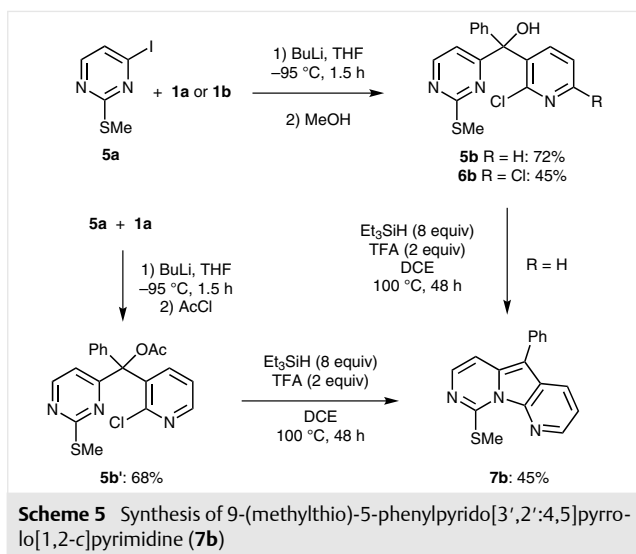
We next considered the formation of 4-methylated 2-chloropyrimidine from **2** and its trapping. The pyrimidine **2** being prone to nucleophilic attacks,<sup>6</sup> we first tried to use the base prepared in situ by mixing ZnCl<sub>2</sub>·TMEDA and LiTMP in a 1:3 ratio,<sup>7</sup> and supposed to be a 1:1 LiTMP·2LiCl(±TMEDA)–Zn(TMP)<sub>2</sub> mixture.<sup>8</sup> 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,<sup>9</sup> 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-Methylated 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 CdCl<sub>2</sub>·TMEDA (0.5 equiv) and LiTMP (1.5 equiv).<sup>10</sup> 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 the THF at –95 °C, as previously documented by Morris,<sup>3b,h,4</sup> 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,<sup>4</sup> 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 aryl(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** Synthesis of the Triaryl Methanols **4b** and **5b–i**

Reaction: **5a** + **1** → **4b** or **5b–i**  
 Conditions: 1) BuLi, THF, -95 °C, 1.5 h; 2) hydrolysis

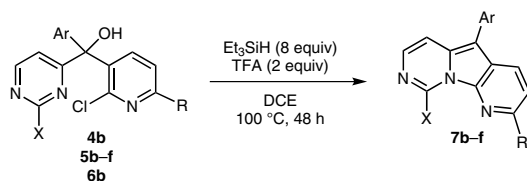
4a: X = Cl  
 5a: X = SMe

Entry	Substrate X	<b>1</b>	Product	Yield (%)
1	<b>4a</b> Cl	<b>1a</b>	<b>4b</b>	24
2	<b>5a</b> SMe	<b>1a</b>	<b>5b</b>	72
3	<b>5a</b> SMe	<b>1c</b>	<b>5c</b>	70

Table 1 (continued)

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

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.

**Table 2** Synthesis of the Tricycles **7b–f**

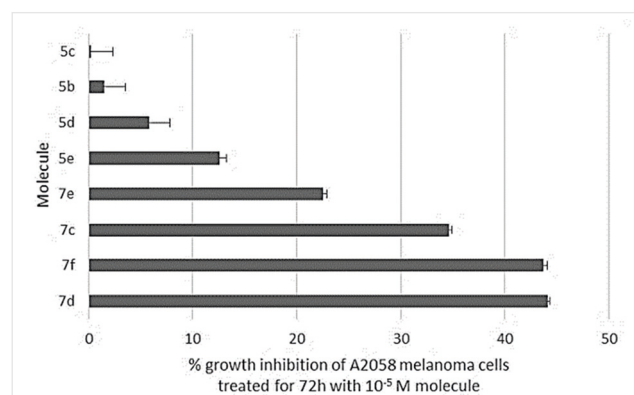
Entry	Substrate X, R	Product	Yield (%)
1	<b>4b</b> Cl, H		0 <sup>a</sup>
2	<b>5b</b> SMe, H		45
3	<b>5c</b> SMe, H		23
4	<b>5d</b> SMe, H		36
5	<b>5e</b> SMe, H		18
6	<b>5f</b> SMe, H		21
7	<b>6b</b> SMe, Cl		0 <sup>a</sup>

<sup>a</sup> Only 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.<sup>2a</sup> This chemical scaffold was consequently used to design new inhibitors of CDK.<sup>11</sup> 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  $\text{sp}^3$  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.<sup>1a,b</sup> The nature of the ring



**Figure 1** Antiproliferative activity of the compounds **5b–e** and **7c–f** in A2058 human melanoma cells grown for 72 h in a cell-culture medium containing  $10^{-5}$  M molecule

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.<sup>1c</sup> Moreover, the presence of ring nitrogens or/and amino function is also critical for CDK inhibition.<sup>2a</sup>

As a conclusion, 2-substituted pyrimidines could be functionalized at their 4-position by using a lithium–metal TMP-based deprotonating agent.<sup>12–14</sup> 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>.

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- (12) **2-Chloro- $\alpha$ -(2-chloro-3-pyridyl)- $\alpha$ -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 at  $-60\text{ }^{\circ}\text{C}$  before introduction of a cooled solution of 2-chloropyrimidine (**2**, 0.11 g, 1.0 mmol) in THF (2 mL). After 2 h at  $-40\text{ }^{\circ}\text{C}$ , a solution of the ketone **1a** (0.26 g, 1.2 mmol) in THF (4 mL) was added at  $-60\text{ }^{\circ}\text{C}$ . The mixture was stirred overnight at r.t. before addition of  $\text{H}_2\text{O}$  (0.5 mL) and dilution with EtOAc (20 mL). The organic layer was dried over  $\text{MgSO}_4$ , 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  $90\text{ }^{\circ}\text{C}$ .  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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:  $m/z$  calcd for  $\text{C}_{16}\text{H}_{11}^{35}\text{Cl}_2\text{N}_3\text{NaO}$  [ $M + \text{Na}$ ] $^+$ : 354.0177; found: 354.0178.
- (13) **4-Iodo-2-(methylthio)pyrimidine (5a)**  
To a stirred, cooled ( $0\text{ }^{\circ}\text{C}$ ) 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,  $\text{ZnCl}_2\text{-TMEDA}^7$  (0.26 g, 1.0 mmol). The mixture was stirred for 15 min at  $0\text{ }^{\circ}\text{C}$  before introduction of 2-(methylthio)pyrimidine (**3**, 0.25 g, 2.0 mmol). After 2 h at this temperature, a solution of  $\text{I}_2$  (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  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL) and extraction with EtOAc ( $3 \times 20$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ , 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).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.54 (s, 3 H), 7.40 (d, 1 H,  $J$  = 5.1 Hz), 8.00 (d, 1 H,  $J$  = 5.1 Hz) ppm.  
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