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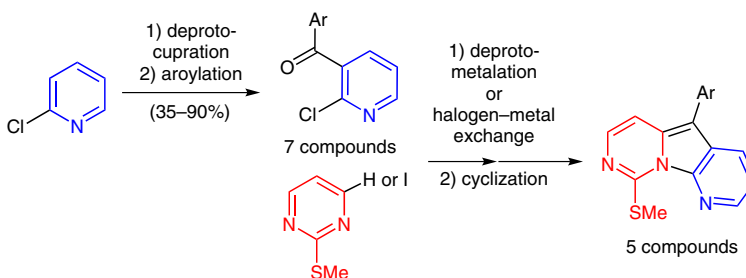
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Azine and Diazine Functionalization Using 2,2,6,6-Tetramethylpiperidino-Based Lithium–Metal Combinations: Application to the Synthesis of 5,9-Disubstituted Pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidines

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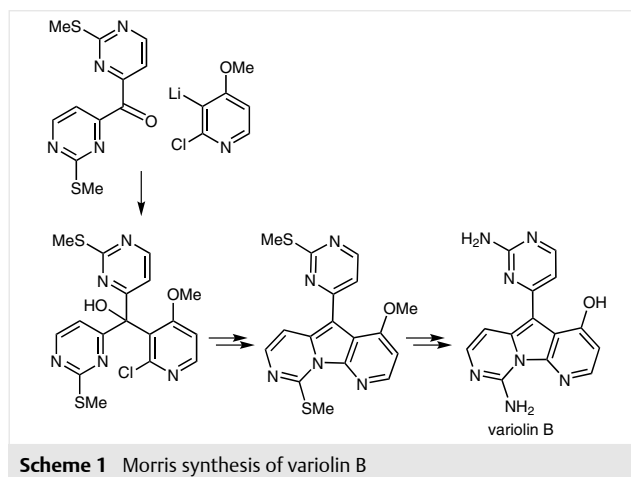
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Abstract The synthesis of triaryl methanols was investigated by reacting different 4-metalated 2-substituted pyrimidines with diaryl ketones, the latter being generated by deprotocupration–arylation of azine and diazine substrates. Cyclization of the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

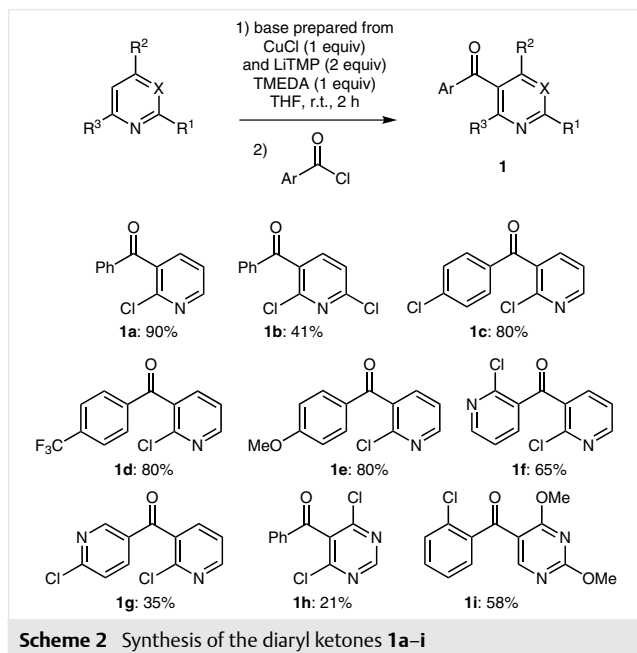
Key words diaryl ketone, pyrimidine, deprotometalation, mixed-metal amide, variolin analogue

Variolins are a family of marine alkaloids isolated from the Antarctic sponge *Kirkpatrickia variolosa*.¹ 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.^{1a,2} Several total syntheses of variolin B and analogues have been reported.^{2b,3} In the convergent synthesis of Morris,^{3b,3h,4} 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).



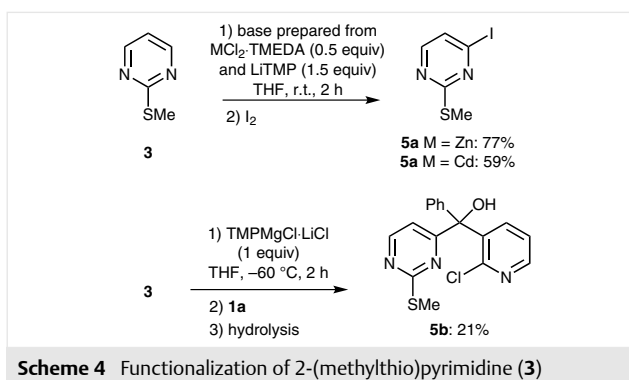
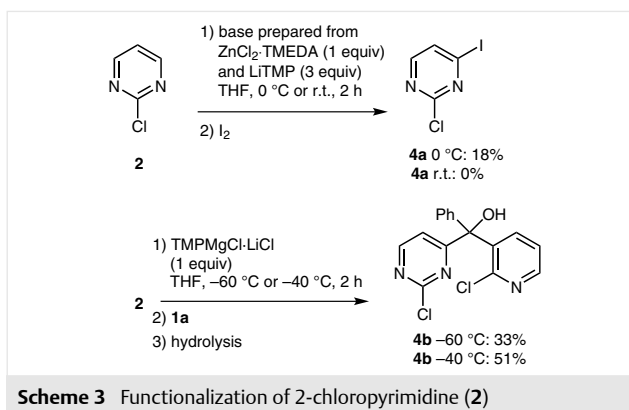
Because of our interest in the synthesis of diaryl ketones by deprotocupration–arylation,⁵ we decided to evaluate the reactivity of these ketones toward different 4-metalated 2-substituted pyrimidines in order to reach different triaryl methanols. Thus, the required diaryl ketones were prepared from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



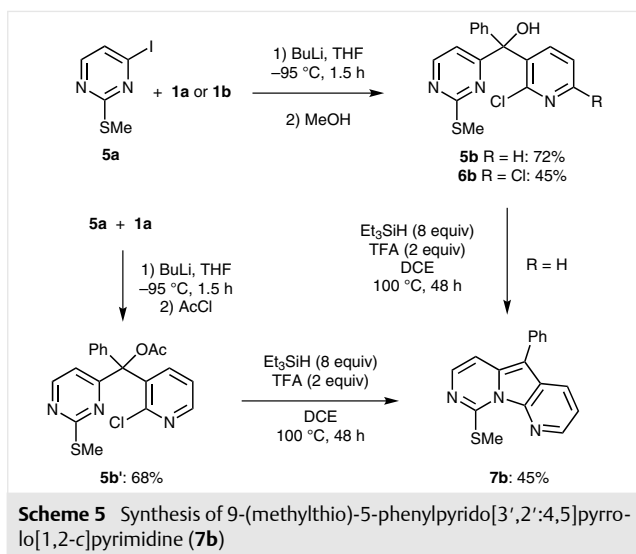
We next considered the formation of 4-methylated 2-chloropyrimidine from **2** and its trapping. The pyrimidine **2** being prone to nucleophilic attacks,⁶ we first tried to use the base prepared in situ by mixing ZnCl₂·TMEDA and LiTMP in a 1:3 ratio,⁷ and supposed to be a 1:1 LiTMP·2LiCl(±TMEDA)–Zn(TMP)₂ mixture.⁸ 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,⁹ 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 CdCl₂·TMEDA (0.5 equiv) and LiTMP (1.5 equiv).¹⁰ 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,^{3b,h,4} 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,⁴ 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

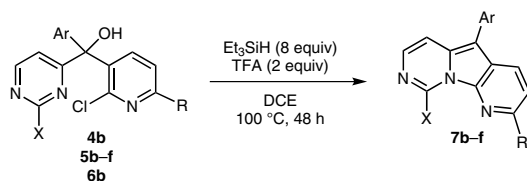
4a: X = Cl
 5a: X = SMe

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

Table 1 (continued)

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

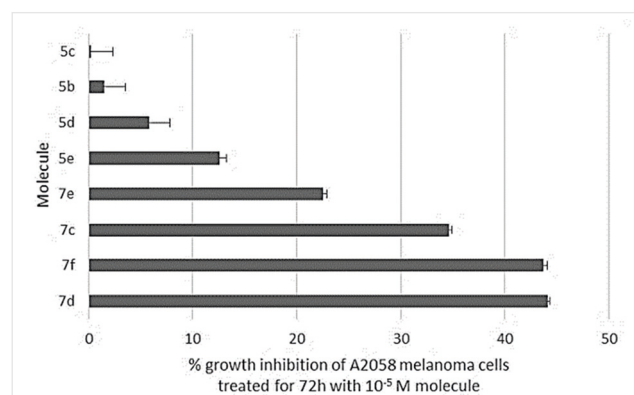
Entry	Substrate X, R	Product	Yield (%)
1	4b Cl, H	 7a	0 ^a
2	5b SMe, H	 7b	45
3	5c SMe, H	 7c	23
4	5d SMe, H	 7d	36
5	5e SMe, H	 7e	18
6	5f SMe, H	 7f	21
7	6b SMe, Cl	 7g	0 ^a

^a 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.^{2a} This chemical scaffold was consequently used to design new inhibitors of CDK.¹¹ 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 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.^{1a,b} 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.^{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

- (1) (a) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987. (b) Trimurtulu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993. (c) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080.
- (2) (a) Simone, M.; Erba, E.; Damia, G.; Vikhanskaya, F.; Di Francesco, A. M.; Riccardi, R.; Bailly, C.; Cuevas, C.; Fernandez Sousa-Faro, J. M.; D'Incalci, M. *Eur. J. Cancer* **2005**, *41*, 2366. (b) Fresneda, P. M.; Delgado, S.; Francesch, A.; Manzanares, I.; Cuevas, C.; Molina, P. *J. Med. Chem.* **2006**, *49*, 1217.
- (3) (a) Alvarez, M.; Fernandez, D.; Joule, J. A. *Tetrahedron Lett.* **2001**, *42*, 315. (b) Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, *42*, 8697. (c) Molina, P.; Fresneda, P. M.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2002**, *43*, 1005. (d) Molina, P.; Fresneda, P. M.; Delgado, S. *J. Org. Chem.* **2003**, *68*, 489. (e) Ahaidar, A.; Fernandez, D.; Danelon, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Alvarez, M. *J. Org. Chem.* **2003**, *68*, 10020. (f) Ahaidar, A.; Fernandez, D.; Perez, O.; Danelon, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Alvarez, M. *Tetrahedron Lett.* **2003**, *44*, 6191. (g) Mendiola, J.; Baeza, A.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2004**, *69*, 4974. (h) Anderson, R. J.; Hill, J. B.; Morris, J. C. *J. Org. Chem.* **2005**, *70*, 6204. (i) Baeza, A.; Mendiola, J.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **2008**, *49*, 4073. (j) Baeza, A.; Mendiola, J.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. J. *Eur. J. Org. Chem.* **2010**, 5607. (k) Layek, M.; Syam Kumar, Y.; Islam, A.; Karavarapu, R.; Sengupta, A.; Halder, D.; Mukkanti, K.; Pal, M. *MedChemComm* **2011**, *2*, 478.
- (4) Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, *42*, 311.
- (5) For a review on the topic, see: Harford, P. J.; Peel, A. J.; Chevallier, F.; Takita, R.; Mongin, F.; Uchiyama, M.; Wheatley, A. E. H. *Dalton Trans.* **2014**, *43*, 14181.
- (6) See, for example: Wang, X.; Xu, F.; Xu, Q.; Mahmud, H.; Houze, J.; Zhu, L.; Akerman, M.; Tonn, G.; Tang, L.; McMaster, B. E.; Dairaghi, D. J.; Schall, T. J.; Collins, T. L.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2800.
- (7) L'Helgoual'ch, J. M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177.
- (8) García-Álvarez, P.; Mulvey, R. E.; Parkinson, J. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 9668.
- (9) Mosrin, M.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 1468.
- (10) (a) Mongin, F.; Uchiyama, M. *Curr. Org. Chem.* **2011**, *15*, 2340. (b) Armstrong, D. R.; Kennedy, A. R.; Mulvey, R. E.; Parkinson, J. A.; Robertson, S. D. *Chem. Sci.* **2012**, *3*, 2700.
- (11) Bettayeb, K.; Tirado, O. M.; Marionneau-Lambot, S.; Ferandin, Y.; Lozach, O.; Morris, J. C.; Mateo-Lozano, S.; Drueckes, P.; Schaechtele, C.; Kubbutat, M. H. G.; Liger, F.; Marquet, B.; Joseph, B.; Echalié, A.; Endicott, J. A.; Notario, V.; Meijer, L. *Cancer Res.* **2007**, *67*, 8325.
- (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 at -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 H_2O (0.5 mL) and dilution with EtOAc (20 mL). The organic layer was dried over 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°C . $^1\text{H NMR}$ (300 MHz, CDCl_3): 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. $^{13}\text{C NMR}$ (75 MHz, CDCl_3): 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 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°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°C before introduction of 2-(methylthio)pyrimidine (**3**, 0.25 g, 2.0 mmol). After 2 h at this temperature, a solution of 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 (3×20 mL). The combined organic layers were dried over 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). ^1H NMR (300 MHz, CDCl_3): 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.
(14) Majeed, A. J.; Antonsen, O.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, 45, 993.