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New efficient access to thieno[3,2-*b*]pyridine derivatives via regioselective lithiation of 3-methylthiopyridine

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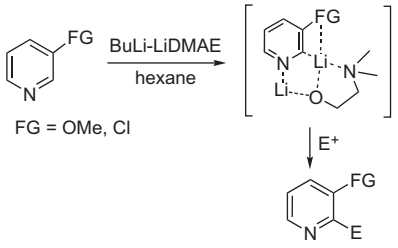
Abstract—The synthesis of thieno[3,2-*b*]pyridines was achieved using a three-step process allowing the construction of the thiophenic ring with 17–34% overall yields. The key step was the regioselective lithiation–bromination of the 3-methylthiopyridine induced by BuLi–LiDMAE superbase followed by Sonogashira coupling and halogenocyclization producing the fused heterocycles.

1. Introduction

Due to their isosterism with indolopyridines or isoquinolines, thienopyridines have attracted much attention because of their potential biological activity as antipsychotics,[1] antibacterians,[2] LH receptor agonists,[3] antitumoral agents[4] or Src kinase inhibitors.[5] Possessing a π-electron rich thiophene ring and a π-electron deficient pyridine ring, these annelated aromatic heterocycles are also of general interest for the chemistry of ligands and theoretical organic chemistry.[6]

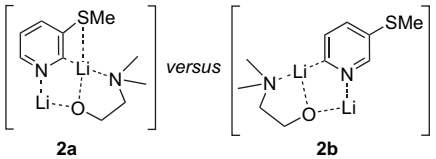
Generally, these fused heterocyclic compounds are prepared by the construction of the pyridinic ring from appropriate substituted thiophene derivatives. These methods suffer from disadvantage of limited access to starting materials, low-functional compatibility and/or long-multistep sequences.[7] In this context, our group is now interested in the development of short polycyclic syntheses[8] based on the selective functionalization of aza-π-deficient heterocycles, such as pyridines, allowing the opportune garlanding for subsequent cyclization.

Some of our previous investigations,[9,10] exhibited the usefulness of the monometallic BuLi–LiDMAE superbase (DMAE: 2-(dimethylamino)ethanol) in apolar solvents to perform regioselective C-2-lithiation of 3-chloro and 3-methoxypyridines. The exclusive C-2-metallation was explained by a strong complexation of lithium by heteroatom (Cl or O), pyridine nitrogen and dimethyl-aminoethoxide in a specific lithiated aggregate (Scheme 1).



Scheme 1. Selective functionalization of 3-methoxy and 3-chloropyridines induced by BuLi–LiDMAE superbase.

In this paper, we focused our attention on regioselective functionalization of 3-methylthiopyridine **1** to evaluate the potential cooperative effect of sulfur atom during the metallation step (Scheme 2). In a synthetic context, the introduction of functionalities at C-2 versus C-6 on the pyridine ring of sulfur containing derivatives could constitute the key step of an alternative and rapid route to functionalized thieno[3,2-*b*]pyridines (Scheme 3).



Scheme 2. Potential cooperative effect of sulfur atom during metallation.

Keywords: Thieno[3,2-*b*]pyridine; Regioselective lithiation; BuLi–LiDMAE superbase; Sonogashira coupling; Halogenocyclization.
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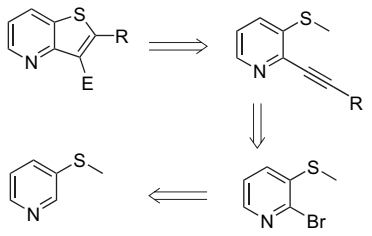


Scheme 3. Access to functional thieno[3,2-*b*]pyridines.

2. Results and discussion

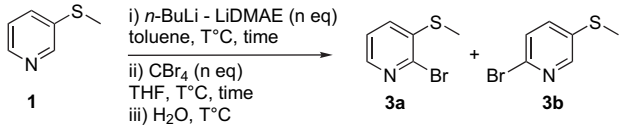
The reactivity of 3-methylthiopyridine **1** was first investigated under various metallation and condensation conditions to evaluate an efficient and regioselective functionalization (i.e., C-2 vs C-6). As mentioned in previous works,[9,10] apolar solvents such as hexane or toluene have to be used to allow a strong aggregation between BuLi–LiDMAE and pyridine substrates. Due to the lack of solubility of **1** in hexane we chose to use toluene as metallation solvent.[11] The expected 2- and 6-lithiopyridine intermediates (**2a** and **2b**) resulting from an α-lithiation process were trapped by tetrabromomethane (CBr_4) as electrophile in THF to produce the stable bromide derivatives **3a** and **3b**.[11]

In Table 1, we report the more significant results of this preliminary study. At first, it appeared to us that standard conditions used with 3-chloropyridine (3 equiv of superbase at −45 °C and hydrolysis at −20 °C, Entry 1) only conducted to poor yields (31%) due to some degradation. However, it was also noticed that the selectivity of **3a/3b** increased when hydrolysis was conducted at −45 °C (Entry 2). We then decided to focus our attention on temperatures of metallation, condensation and hydrolysis steps. At −80 °C, an interesting increase of yield was obtained (51%, Entry 3) showing that a lower temperature of metallation limited the degradation. However, in the same time, we observed a slight decrease in the selectivity. In contrast at −95 °C, the selectivity was increased to 90/10 and the conversion was limited to 65% (Entry 4). At this temperature the use of an excess (6 equiv) of superbase allowed us to combine a high regioselectivity and a yield (89/11 and 73%, respectively, Entry 6). In these conditions, we determined an optimal 1 h condensation time (condensation times up to 2 h led to degradation of lithiated species). Entries 7–10 finally confirmed that with the same excess of superbase, extended or shorter metallation times as well as a higher temperature conducted to a decrease in both yield and selectivity. In agreement with this preliminary study, we have set the best conditions for the regioselective functionalization of 3-methylthiopyridine **1** as follows: 6 equiv of base in non complexing toluene, a metallation time of 4 h and a condensation time of 1 h, all the protocol having to be conducted at −95 °C.

As the regioselectivity of this reaction is concerned, our results confirm the hypothesis of the sulfur atom chelating effect on the basic system, even if, as expected, the complexing influence appears less strong than in 3-chloro or 3-methoxypyridines.[9] It must be noted that no trace of 4-bromo-3-methylpyridine was detected so, this emphasizes the strong aggregation between BuLi–LiDMAE superbase and pyridine moieties, which dictate the selectivity of lithiation.

The versatility and the synthetic value of our methodology were next examined by the introduction of various representative electrophiles at C-2 and/or C-6 positions (Table 2). The expected compounds **4**–**8** were obtained in moderate to good isolated yields (45–68% overall). Chloride, sulfide and deuterium are selectively introduced in C-2 position due to the expected chelating effect of the sulfur atom on the basic system during the deprotonation step. In contrast, despite a good conversion rate, iodide derivatives were obtained in low 11% yield (not reported here) due to a great instability of the formed products. It can be assumed that the

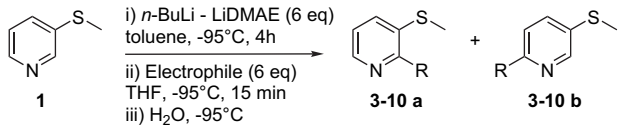
Table 1. Optimization of the functionalization of 3-methylthiopyridine **1**[a]



Entry	Metallation conditions			Halogenation conditions		Hydrolysis	Yields[b] (%)	Results[b,c] ratio
	Base (equiv)	*T* (°C)	*t* (h)	CBr_4 (equiv)	*T* (°C)	*T* (°C)	(**3a+3b**)	(**3a/3b**)
1	3	−45	1	3	−45	−20[a]	31	77/23
2	3	−45	1	3	−45	−45	29	86/14
3	3	−80	4	3	−80	−20[a]	51	82/18
4	3	−95	4	3	−95	−95	23[d]	90/10
5	4	−95	4	4	−95	−95	65	72/28
6	6	−95	4	6	−95	−95	73	89/11
7	6	−95	8	6	−95	−95	53	87/13
8	6	−95	2	6	−95	−95	44	84/16
9	6	−80	4	6	−80	−80	61	82/18
10	6	−80	1	6	−80	−80	48	83/17

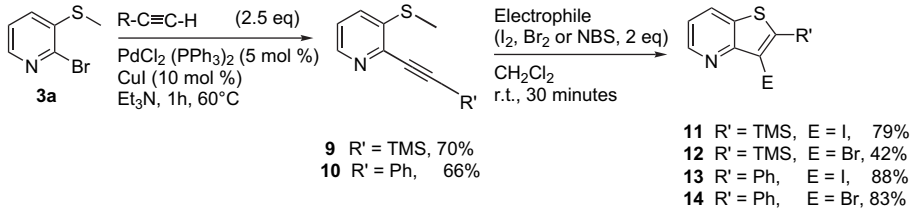
[a] Reaction temperature (−45 or −80 °C) was risen to −20 °C in 15 min.
[b] GC yields and selectivity ratio relative to an internal standard.
[c] Total conversion of **1** was observed.
[d] Conversion rate of reaction was limited to 65%.

Table 2. Scope and limitation of the electrophile[a]



Entry	Electrophile	R	Total isolated yields[b]	Ratio[c]	Isolated yields[b]	
			a+b (%)	**a/b**	Isomer **a** (%)	Isomer **b** (%)
1	CBr_4	Br	68	9/1	**3a** (59%)	**3b** (9%)
2	C_2Cl_6	Cl	65	8/2	**4a** (50%)	**4b** (15%)
3	I_2	I	11	8/2	**5a+5b**[c,d,e]	
4	Me_2S_2	SMe	49	7/3[c]	**6a+6b**[c,e]	
5	Ph_2S_2	SPh	63	9/1	**7a** (57%)	**7b** (6%)
6	TESCl	$Si(Et)_3$	52	1/9	**8a+8b**[b,c]	
7	DCl/D_2O	D	—	8/2	**9a**[c] (80%)	**9b**[c](20%)
8	PhCHO	CH(OH)Ph	45	2/8	**10a** (8%)	**10b** (37%)

[a] Reactions performed on 1.33 mmol of **1**.
[b] Isolated yields after silica gel chromatography.
[c] GC or ^1H NMR yields.
[d] Rapid degradation of the products.
[e] Isolated as a mixture of regioisomers **a** and **b**.



Scheme 4. Synthesis of thieno[3,2-*b*]pyridine derivatives.

iodopyridines might be in situ formed and quickly attacked by remaining *n*-BuLi or lithium alkoxides. On an other hand, phenylmethanol or triethylsilyl moieties were introduced with a reverse regioselectivity (**7b** and **8b** formed as major products). This inverse selectivity showed the competition between a chelating effect and a steric hindrance of the electrophile moiety. Indeed, it may be postulated that the approach of the sterically hindered electrophile to the lithiated pyridine aggregate in C-2 position was more difficult than in C-6 one. This led us to conclude that the condensation step is strongly controlled by the formation of the product and that the complexation effect of sulfur part is slight.

In a synthetic context, the silyl product **8b** could have been involved in Hiyama coupling.[12] However, they are only obtained as a crude intractable and unstable mixture, which is rapidly degraded in the reaction medium not allowing further additional range of functionalization by this way of synthesis.

We next turned our efforts towards the functionalization of formed halogenated derivatives. Starting from the readily available 2-bromo-3-methylthiopyridine **3a**, a two step approach to functionalized thienopyridines has then been examined involving Sonogashira coupling with terminal acetylenes (trimethysilylacetylene or phenylacetylene) followed by an electrophilic cyclization.[13] This scheme of synthesis leads to particularly quite reaction times and very easy setting to access to thieno[3,2-*b*]pyridine derivatives (Scheme 4).

In a first step, acetylenic reagents were successfully coupled in Sonogashira reactions using $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10 mol %) in Et_3N as solvent and base. Electrophilic cyclization was next performed using iodine or bromine as electrophile. 2-Alkynyl-3-methylthiopyridines **9**–**10** reacted efficiently to produce **11**, **13** and **14** in excellent yields (79–88%). In most cases, reaction time did not exceed 30 min at room temperature. It is noteworthy that reactions with Br_2 gave different results from those obtained with I_2. Indeed, no trace of silyl bromide derivative **12** was detected using Br_2 as electrophile while **14** was obtained with good yield. When Br_2 was changed by NBS and the reaction mixture stirred overnight at room temperature, expected cyclization product **12** were obtained in acceptable 42% yield. This result could be explained by a rapid bromodesilylation producing an unstable 2,3-dibromothieno[3,2-*b*]pyridine. Thieno[3,2-*b*]pyridine derivatives **11**, **12**, **13** and **14** were then prepared with overall yields of 33, 17, 34 and 32%, respectively.

3. Conclusion

In summary, a new synthesis of thieno[3,2-*b*]pyridines have been prepared from 3-methylthiopyridine in moderate to good yields. We believe that the three steps approach based on the construction of thiophenic ring is a useful alternative to classical methods and should prove quite useful in heterocyclic synthesis. We are currently aiming to expand this methodology for the use of other functionalized fused polyheterocycles.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded at 400 or 250 and 100 MHz, respectively, with $CDCl_3$ as solvent and TMS as internal standard (for ^1H NMR). HRMS were determined at the Service Central d'Analyse of the CNRS at Vernaison (France).

4.2. Materials and solvents

All reagents were commercially available and were purified by distillation when necessary. *n*-BuLi was used as a commercial 1.6 M solution in hexanes. 2-(Dimethylamino) ethanol (DMAE) was distilled and stored over molecular sieves before use. Toluene and THF were distilled and stored on sodium wire before use.

4.3. Preparation of 3-methylthiopyridine (1)

A solution of anhydrous THF (80 mL) was cooled at −80 °C and *t*-BuLi (31 mL, 54 mmol) was added dropwise under a nitrogen atmosphere. Then, a solution of 3-bromopyridine (4.230 g, 27 mmol) in THF (5 mL) was added dropwise. After stirring for 30 min at −80 °C, the reaction medium was cooled at −95 °C and dimethyldisulfur (6 mL, 67 mmol) in THF (5 mL) was added. After stirring for 1 h at −95 °C, hydrolysis was performed at −20 °C with H_2O (30 mL). The aqueous phase was extracted with ethyl acetate (20 mL). After drying ($MgSO_4$), filtration and solvents evaporation, the crude product was purified by column chromatography on a silica gel (Geduran Si 60, 0.063–0.200 mm). The spectroscopic data are in conformity with literature.

4.4. General procedure for functionalization of 3-methylthiopyridine (1)

A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in anhydrous toluene (15 mL) was cooled at ca. −5 °C, and *n*-BuLi (10 mL, 16 mmol) was added dropwise under a nitrogen atmosphere. After 15 min. at 0 °C, the reaction medium was cooled at −95 °C. 3-Methylthiopyridine **1** (166 mg, 1.33 mmol) in anhydrous toluene (5 mL) was added dropwise. After stirring for 4 h at −95 °C, a solution of the appropriate electrophile (8 mmol) in anhydrous THF (10 mL) was added dropwise. After stirring at −95 °C during the appropriate time, hydrolysis was performed at this temperature with H_2O (30 mL). The aqueous phase was extracted with ethyl acetate (20 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on a silica gel (0.063–0.200 mm) with hexane/ethyl acetate mixtures as eluent.

4.4.1. 2-Bromo-3-methylthiopyridine (3a) and 6-bromo-3-methylthiopyridine (3b). Compounds **3a** and **3b** were prepared according to the general method described herein with CBr_4 (2.653 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **3a** (159 mg, 59%) and **3b** (24 mg, 9%), yield in **3a+3b** (183 mg, 68%) with a regioselectivity **3a/3b**: 9/1.

4.4.1.1. 2-Bromo-3-methylthiopyridine (3a). Brown gummy solid; ^1H NMR δ_H 2.50 (s, 3H), 7.40 (m, 2H), 8.24 (d, J=2 Hz, 1H); ^{13}C NMR δ_C 15.43, 123.16, 132.82, 140.69, 145.09, 161.80; IR (NaCl) ν 2920, 1542, 1447, 1349, 1113, 1078, 1011, 820, 754; MS (EI) *m/z* 205 (99), 203 (100), 190 (7), 124 (52), 109 (74), 97 (66), 82 (46), 76 (13), 57 (13), 51 (19); HRMS (ESI^+) Calculated for C_6H_6BrNS=202.9405, found $[M+H]^+$=203.9491.

4.4.1.2. 6-Bromo-3-methylthiopyridine (3b). White solid; mp 54–56 °C; ^1H NMR δ_H 2.50 (s, 3H), 7.27 (dt, J=4.5, 1.0 Hz, 1H), 7.39 (dd, J=7.9, 1.7 Hz, 1H), 8.13 (dd, J=4.8, 1.7 Hz, 1H); ^{13}C NMR δ_C 15.99, 127.97, 135.33, 136.95, 138.48, 147.90; IR (NaCl) ν 2920, 1542, 1447, 1349, 1113, 1078, 1011, 820, 754; MS (EI) *m/z* 205 (99), 203 (100), 190 (7), 124 (52), 109 (74), 97 (66), 82 (46), 76 (13), 57 (13), 51 (19).

4.4.2. 2-Chloro-3-methylthiopyridine (4a) and 6-chloro-3-methylthiopyridine (4b). Compounds **4a** and **4b** were prepared according to the general method described herein with C_2Cl_6 (1.896 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **4a** (106 mg, 50%) and **4b** (32 mg, 15%), yield in **4a+4b** (138 mg, 65%) with a regioselectivity **4a/4b**: 8/2.

4.4.2.1. 2-Chloro-3-methylthiopyridine (4a).[14] Pale yellow gummy solid; ^1H NMR δ_H 2.44 (s, 3H), 7.19 (dt, J=4.7 Hz, 1H), 7.42 (dd, J=7.8, 1.3 Hz, 1H), 8.11 (dd, J=4.7, 1.5 Hz, 1H); ^{13}C NMR δ_C 14.88, 122.90, 133.28, 136.13, 144.61, 147.96; IR (NaCl) ν 2924, 1547, 1449, 1354, 1120, 1014, 823, 726; MS (EI) *m/z* 162 (8), 161 (31), 159 (100), 146 (6), 144 (15), 123 (26), 122 (13), 117 (11), 97 (7), 96 (22), 83 (13), 82 (18), 78 (17), 76 (8), 69 (11), 64 (6), 60 (6), 51 (12).

4.4.2.2. 6-Chloro-3-methylthiopyridine (4b). Pale yellow gummy solid; ^1H NMR δ_H 2.51 (s, 3H), 7.25 (dd, J=8.0, 1H), 7.55 (dd, J=8.3, 2.6 Hz, 1H), 8.27 (d, J=2.4 Hz, 1H); ^{13}C NMR δ_C 16.18, 124.24, 134.64, 137.33, 147.58, 148.37; IR (NaCl) ν 2924, 1547, 1449, 1354, 1120, 1014, 823, 726; MS (EI) *m/z* 162 (8), 161 (31), 159 (100), 146 (6), 144 (15), 123 (26), 122 (13), 117 (11), 97 (7), 96 (22), 83 (13), 82 (18), 78 (17), 76 (8), 69 (11), 64 (6), 60 (6), 51 (12).

4.4.3. 3-Methylthio-2-phenylthiopyridine (5a) and 3-methylthio-6-phenylthiopyridine (5b). Compounds **5a** and **5b** were prepared according to the general method described herein with Ph_2S_2 (1.744 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **5a** (177 mg, 57%) and **5b** (18 mg, 6%), yield in **5a+5b** (195 mg, 63%) with a regioselectivity **5a/5b**: 9/1.

4.4.3.1. 3-Methylthio-2-phenylthiopyridine (5a). Pale yellow gummy solid; ^1H NMR δ_H 2.53 (s, 3H), 7.04 (dt, J=4.8 Hz, 1H), 7.41 (m, 3H), 7.49 (dd, J=7.8, 1.5 Hz, 1H), 7.55 (m, 2H), 8.20 (dd, J=4.7, 1.5 Hz, 1H); ^{13}C

NMR δ_C 16.16, 121.05, 128.50, 129.19, 134.14, 134.32, 146.33, 151.90, 157.10; IR (NaCl) ν 2921, 1561, 1439, 1352, 1131, 747, 690; MS (EI) *m/z* 234 (14), 233 (M^+, 56), 232 (74), 218 (100), 217 (32), 186 (47), 172 (12), 115 (12), 82 (39), 69 (35), 65 (38), 51 (10); HRMS (ESI^+) Calculated for $C_{12}H_{11}NS_2$=233.0334, found $[M+H]^+$= 234.0405.

4.4.3.2. 3-Methylthio-6-phenylthiopyridine (5b). Pale yellow gummy solid; ^1H NMR δ_H 2.48 (s, 3H), 6.89 (dd, *J*=8.4 Hz, 1H), 7.42 (m, 4H), 7.59 (m, 2H), 8.37 (d, *J*=2.1 Hz, 1H); ^{13}C NMR δ_C 16.19, 121.46, 128.52, 129.17, 134.10, 135.74, 147.93, 151.30, 158.64; IR (NaCl) ν 2921, 1561, 1439, 1352, 1131, 747, 690; MS (EI) *m/z* 234 (14), 233 (M^+, 56), 232 (74), 218 (100), 217 (32), 186 (47), 172 (12), 115 (12), 82 (39), 69 (35), 65 (38), 51 (10).

4.4.4. Procedure for C-2 and C-6 functionalization of 3-methylthiopyridine (1) with deuterium. A solution of DMAE (0.8 mL, 8 mmol) in toluene (15 mL) was cooled at ca. −5 °C, and *n*-BuLi (10 mL, 16 mmol) was added dropwise under a nitrogen atmosphere. After 15 min at 0 °C, the reaction medium was cooled at −95 °C. 3-Methylthiopyridine **1** (166 mg, 1.33 mmol) in toluene (5 mL) was added dropwise. After 4 h of stirring at −95 °C, a solution MeOD (2 mL, 49 mmol) in THF (10 mL) was added dropwise. After 1 h of stirring at −95 °C the solution was dried ($MgSO_4$), filtrated and solvents were evaporated. The ^1H NMR data of the crude mixture allowed to determine a regioselectivity **6a/6b**: 8/2.

4.4.5. (3-Methylthiopyridin-2-yl)phenylmethanol (7a) and (3-methylthiopyridin-6-yl)phenylmethanol (7b). Compounds **7a** and **7b** were prepared according to the general method described herein with PhCHO (1.744 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **7a** (25 mg, 8%) and **7b** (114 mg, 37%), yield in **7a+7b** (139 mg, 45%) with a regioselectivity **7a/7b**: 2/8.

4.4.5.1. (3-Methylthiopyridin-2-yl)phenylmethanol (7a). White solid; mp 60–62 °C; ^1H NMR δ_H 2.31 (s, 3H), 5.91 (s, 1H), 7.28 (m, 6H), 7.50 (dd, *J*=8.1 Hz, 1H), 8.40 (dd, *J*=4.6 Hz, 1H); ^{13}C NMR δ_C 29.82, 74.75, 121.49, 127.10, 128.07, 128.37, 128.76, 128.92, 134.63, 136.07, 145.50, 157.89; IR (NaCl) ν 3391, 2921, 1421, 1393, 1038, 699, 607; MS (EI) *m/z* 233 (5), 232 (15), 231 (M^+, 80), 216 (29), 182 (25), 155 (54), 154 (50), 124 (33), 110 (27), 105 (28), 79 (83), 77 (100), 51 (45); HRMS (ESI^+) Calculated for $C_{13}H_{13}NOS$=231.0719, found $[M+H]^+$= 232.0791.

4.4.5.2. (3-Methylthiopyridin-6-yl)phenylmethanol (7b). White solid; mp 70–72 °C; ^1H NMR δ_H 2.50 (s, 3H), 5.75 (s, 1H), 7.10 (dd, *J*=8.2 Hz, 1H), 7.28 (m, 5H), 7.52 (dd, *J*=8.3, 2.2 Hz, 1H), 8.45 (d, *J*=1.9 Hz, 1H); ^{13}C NMR δ_C 15.80, 72.40, 123.25, 127.09, 127.71, 127.90, 128.12, 128.49, 128.67, 134.44, 142.15, 143.87, 157.58; IR (NaCl) ν 3391, 2921, 1421, 1393, 1038, 699, 607; MS (EI) *m/z* 233 (5), 232 (15), 231 (M^+, 80), 216 (29), 182 (25), 155 (54), 154 (50), 124 (33), 110 (27), 105 (28), 79 (83), 77 (100), 51 (45).

4.5. Procedure for the palladium-catalyzed formation of 2-(1-alkynyl)-3-methylthiopyridines (9–10)

To a solution of Et_3N (10 mL), $PdCl_2(PPh_3)_2$ (0.070 g, 5 mol %), 2-bromo-3-methylthiopyridine **3a** (0.408 g, 2 mmol) and the appropriate terminal acetylene (5 mmol) (stirring for 5 min beforehand) was added CuI (0.038 mg, 10 mol %) and stirring was continued for another 15 min before flushing with N_2. The mixture was heated to Et_3N reflux and stirred for 1 h. The resulting solution was rapidly washed with a saturated aqueous NH_4Cl solution, and extracted with dichloromethane (2×10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on a silica gel (0.063–0.200 mm) with hexane/ethyl acetate mixtures as eluent.

4.5.1. 2-(2-Trimethylsilylethyn-1-yl)-3-methylthiopyridine (9). Compound **9** was prepared according to the method described herein with trimethylsilylacetylene (0.246 g, 5 mmol) as terminal acetylene. Column chromatography (eluent: hexane/AcOEt 70/30) yielded **9** (0.310 g, 70%) as a brown gummy solid. ^1H NMR δ_H 0.30 (s, 9H), 2.47 (s, 3H), 7.19 (dt, *J*=4.7 Hz, 1H), 7.46 (dd, *J*=8.1, 1.3 Hz, 1H), 8.3 (dd, *J*=4.1 Hz, 1H); ^{13}C NMR δ_C −0.18, 14.69, 101.03, 112.13, 123.24, 128.71, 131.49, 145.30; IR (NaCl) ν 2952, 2157, 1558, 1398, 1247, 1079, 1037, 850, 758, 703; MS (EI) *m/z* 221 (M^+, 55), 206 (97), 190 (17), 176 (29), 130 (14), 84 (100), 51 (14).

4.5.2. 2-(2-Phenylethyn-1-yl)-3-methylthiopyridine (10). Compound **10** was prepared according to the method described herein with phenylacetylene (0.255 g, 5 mmol) as terminal acetylene. Column chromatography (eluent: hexane/AcOEt 70/30) yielded **10** (0.300 g, 66%) as a brown powder; mp 75–77 °C; ^1H NMR δ_H 2.51 (s, 3H), 7.23 (dt, *J*=4.8 Hz, 1H), 7.38 (m, 3H), 7.48 (dd, *J*=8.0 Hz, 1H), 7.65 (m, 2H), 8.36 (dd, *J*=4.6 Hz, 1H); ^{13}C NMR δ_C 14.82, 86.55, 122.35, 123.02, 128.51, 129.26, 131.57, 132.21, 145.51; IR (NaCl) ν 3058, 2918, 2214, 1490, 1410, 1218, 1139, 756, 691; MS (EI) *m/z* 227 (4), 226 (15), 225 (M^+, 65), 224 (100), 223 (53), 222 (11), 209 (8), 191 (8), 180 (8), 150 (11), 148 (39), 139 (13), 111 (13), 77 (13), 51 (13); HRMS (ESI^+) Calculated for $C_{14}H_{11}NS$= 225.0613, found $[M+H]^+$=226.0690.

4.6. Procedure for the iodo- and bromocyclizations

To a solution of 0.25 mmol of the 2-(1-alkynyl)-3-methylthiopyridines **9**–**10** and 3 mL of CH_2Cl_2 was added gradually I_2 or Br_2 (0.5 mmol) in 2 mL of CH_2Cl_2. The reaction mixture was flushed with N_2 and stirred at room temperature for 30 min. The excess of I_2 or Br_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted by CH_2Cl_2 (2×10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on a silica gel (0.063–0.200 mm) with hexane/ethyl acetate mixtures as eluent.

4.6.1. 3-Iodo-2-trimethylsilylthieno[3,2-*b*]pyridine (11). Compound **11** was prepared according to the method described herein with I_2 (127 mg, 0.5 mmol). Column

chromatography (eluent: hexane/AcOEt 70/30) yielded **11** (66 mg, 79%) as a yellow pale solid; mp 79–81 °C; ^{1}H NMR δ_H 0.20 (s, 9H), 6.95 (dt, J=4.5, 1.3 Hz, 1H), 7.81 (dd, J=8.1, 1.4 Hz, 1H), 8.47 (dd, J=4.6, 1.4 Hz, 1H); ^{13}C NMR δ_C 0.05, 91.81, 119.95, 130.73, 148.69; IR (KBr) ν 2924, 1384, 1246, 981, 889, 842, 759, 632; MS (EI) m/z 334 (12), 333 (M^+, 67), 318 (100), 190 (44), 176 (60), 162 (13), 148 (19), 130 (15), 116 (19), 89 (30), 69 (24), 57 (37); HRMS (ESI$^+$) Calculated for $C_{10}H_{12}INSSi$=332.9506, found $[M+H]^+$=333.9580.

4.6.2. 3-Bromo-2-trimethylsilylthieno[3,2-*b*]pyridine (12). Compound **12** was prepared according to the method described herein with NBS (89 mg, 0.5 mmol). The mixture stirred at room temperature overnight. Column chromatography (eluent: hexane/AcOEt 70/30) yielded **12** (30 mg, 42%) as yellow gummy solid; ^{1}H NMR δ_H 0.050 (s, 9H), 7.30 (dt, J=4.5 Hz, 1H), 8.17 (dd, J=8.1 Hz, 1H), 8.80 (dd, J=4.5 Hz, 1H); ^{13}C NMR δ_C 1.64, 29.18, 116.65, 118.81, 129.86, 140.19, 147.58, 153.16; IR (NaCl) ν 2955, 2923, 1389, 1250, 994, 893, 842, 759; MS (EI) m/z 287 (70), 285 (M^+, 70), 272 (98), 270 (100), 190 (67), 176 (28), 148 (40), 130 (20), 89 (20); HRMS (ESI$^+$) Calculated for $C_{10}H_{12}BrNSSi$=284.9644, found $[M+H]^+$= 285.9716.

4.6.3. 3-Iodo-2-phenylthieno[3,2-*b*]pyridine (13). Compound **13** was prepared according to the method described herein with I_2 (127 mg, 0.5 mmol). Column chromatography (eluent: hexane/AcOEt 70/30) yielded **13** (74 mg, 88%) as a yellow gummy solid. ^{1}H NMR δ_H 7.31 (dt, J=4.7 Hz, 1H), 7.50 (m, 3H), 7.73 (m, 2H), 8.12 (dd, J= 8.1, 1.2 Hz, 1H), 8.82 (dd, J=4.6, 1.2 Hz, 1H); ^{13}C NMR δ_C 83.42, 120.06, 128.81, 129.56, 129.94, 130.42, 134.32, 148.50; IR (NaCl) ν 3040, 2924, 2852, 1542, 1479, 1389, 1148, 1073, 785, 750, 694; MS (EI) m/z 338 (13), 337 (M^+, 100), 210 (51), 166 (12), 139 (20), 127 (11), 105 (27), 91 (15), 83 (12), 69 (9), 57 (12); HRMS (ESI$^+$) Calculated for $C_{13}H_8INS$=336.9423, found $[M+H]^+$= 337.9517.

4.6.4. 3-Bromo-2-phenylthieno[3,2-*b*]pyridine (14). Compound **14** was prepared according to the method described herein with Br_2 (0.26 mL, 0.5 mmol). Column chromatography (eluent: hexane/AcOEt 70/30) yielded **14** (60 mg, 83%) as a white solid; mp 110–112 °C; ^{1}H NMR δ_H 7.30 (dt, J=4.6 Hz, 1H), 7.50 (m, 3H), 7.80 (m, 2H), 8.12 (dd, J=8.1, 1.3 Hz, 1H), 8.80 (dd, J=4.6, 1.3 Hz, 1H); ^{13}C NMR δ_C 107.51, 120.01, 128.87, 129.58, 130.47, 132.16, 148.36, 153.27; IR (NaCl) ν 3052, 2926, 1393, 1276, 1074, 894, 754; MS (EI) m/z 291 (85), 289 (M^+, 100), 210 (39), 166 (16), 139 (24), 105 (16); HRMS (ESI$^+$) Calculated for $C_{13}H_8BrNS$=288.9561, found $[M+H]^+$= 289.9647.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.008.

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