A Simple Method for the Synthesis of 3-Arylthieno[2,3-*b*]pyridines via Iodine-Mediated Cyclization of 3-(1-Arylalkenyl)-2-[(1-phenylethyl)sulfanyl]pyridines

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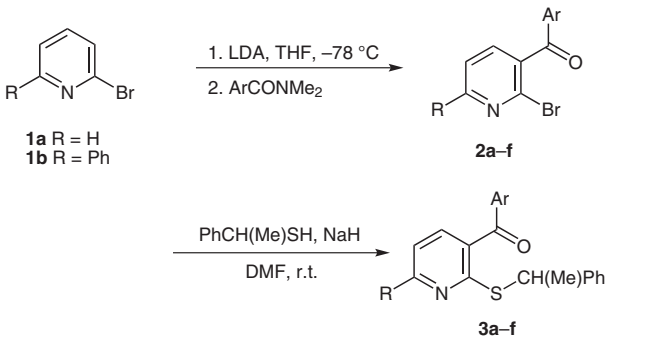
Abstract: 3-Arylthieno[2,3-*b*]pyridines are synthesized in a short four-step sequence from readily available 2-bromopyridines. The final and key step of the reported method involves an iodine-mediated 5-*endo* cyclization of 3-(1-arylalkenyl)-2-[(1-phenylethyl)sulfanyl]pyridines.

Key words: thieno[2,3-*b*]pyridines, iodine, 2-bromopyridines, cyclization, heterocycles

We have recently reported the synthesis of 3-substituted benzo[*b*]thiophenes,[1] the key step in our procedure being the iodine-mediated 5-*endo* cyclization of 2-[(1-phenylethyl)sulfanyl]styrenes. As an extension of this study we now describe a new and simple approach for the synthesis of 3-arylthieno[2,3-*b*]pyridines **5** from readily available 2-bromopyridines, which is based on the reaction of 3-(1-arylalkenyl)-2-[(1-phenylethyl)sulfanyl]pyridines **4** with iodine. Several methods have been reported for the preparation of thieno[2,3-*b*]pyridines,[2] as many derivatives possessing this skeleton have been reported to exhibit varied biological activity.[3] Hence, we have investigated simple and general methods for the synthesis of this class of heterocycles.

As starting materials, 2-bromopyridine (**1a**) was commercially available whilst 2-bromo-6-phenylpyridine (**1b**) was prepared from commercially available 2-phenylpyridine according to the reported procedure.[4] 2-Bromopyridines **1a** and **1b** were first lithiated using lithium diisopropylamide (LDA) in tetrahydrofuran at –78 °C, via the reported procedure,[5] to afford the corresponding 2-bromo-3-lithiopyridines. These were then reacted with various *N*,*N*-dimethylbenzamides to give 3-aroyl-2-bromopyridines **2a**–**f** in moderate yields. Next, the 2-bromo group was substituted with a (1-phenylethyl)sulfanyl group by reaction with 1-phenylethanethiol[6] and sodium hydride in *N*,*N*-dimethylformamide at room temperature to afford aryl 2-[(1-phenylethyl)sulfanyl]pyridin-3-yl ketones **3a**–**f** in good yields, as illustrated in Table 1.

Table 1 Preparation of 2-[(1-Phenylethyl)sulfanyl]pyridin-3-yl Ketones **3a**–**f**



Entry	R	Ar	Yield (%) of **2**	Yield (%) of **3**
a	H	Ph	54	87
b	H	3-MeC_6H_4	56	79
c	H	4-MeC_6H_4	58	81
d	H	3-ClC_6H_4	52	78
e	H	4-ClC_6H_4	63	76
f	Ph	4-MeOC_6H_4	61	86

The transformation of 2-[(1-phenylethyl)sulfanyl]pyridin-3-yl ketones **3** into 3-arylthieno[2,3-*b*]pyridines **5** was carried out according to the procedure shown in Scheme 1. Thus, compounds **3** were converted into the corresponding 3-(1-arylalkenyl)-2-[(1-phenylethyl)sulfanyl]pyridines **4** in good yields on treatment with methylene(triphenyl)phosphorane or ethylidene(triphenyl)phosphorane (Table 2). The subsequent iodine-mediated cyclization of **4** was initially conducted under conditions previously reported for the preparation of benzo[*b*]thiophenes.[1] Unfortunately, we did not obtain the desired products **5** in satisfactory yields; a considerable amount of the starting material was recovered in each case. Further investigation allowed optimization of the reaction conditions for the conversion of **4** into thieno[2,3-*b*]pyridines **5**. Thus, treatment of **4** with three portions each of two molar equivalents of iodine and sodium bicarbonate, at six hour intervals, in acetonitrile at room temperature, and subsequent stirring overnight at the same temperature gave the desired products **5**. Preparative thin-

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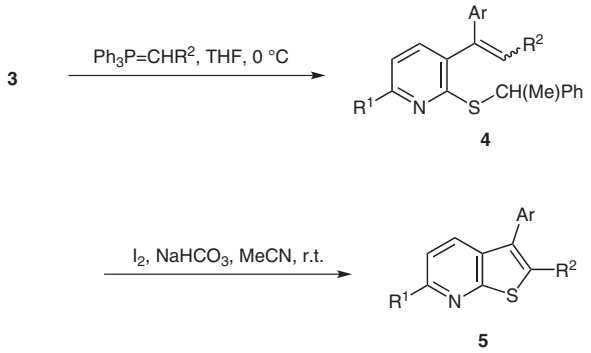
layer chromatography afforded pure thieno[2,3-*b*]pyridines **5** in satisfactory yields (Table 2). However, lower yields of thieno[2,3-*b*]pyridines **5a′** and **5e′** were obtained on cyclization of compounds **4a′** and **4e′** which possess a methyl substituent at the β-position of the alkenyl moiety (entries 2 and 7); these reactions proceeded more sluggishly and gave complex mixtures containing unreacted starting material. The presence of the β-methyl substituent may restrict product formation due to steric hindrance in the cyclization intermediate.



Scheme 1 Synthesis of thieno[2,3-*b*]pyridines **5**

Table 2 Preparation of 3-Arylthieno[2,3-*b*]pyridines **5**

Entry	Substrate	R^2	Yield (%)[a] of **4**	Yield (%)[a] of **5**
1	**3a**	H	**4a** (89)	**5a** (72)
2	**3a**	Me	**4a′** (75)	**5a′** (40)
3	**3b**	H	**4b** (87)	**5b** (75)
4	**3c**	H	**4c** (93)	**5c** (70)
5	**3d**	H	**4d** (86)	**5d** (76)
6	**3e**	H	**4e** (91)	**5e** (67)
7	**3e**	Me	**4e′** (84)	**5e′** (33)
8	**3f**	H	**4f** (86)	**5f** (72)

[a] Yield of isolated product.

Attempts to obtain 3-alkylthieno[2,3-*b*]pyridines failed, because, for example, the precursor (equivalent to **3**) for the synthesis of 3-ethylthieno[2,3-*b*]pyridine could not be prepared using the present method. The reaction of 2-bromopyridin-3-yl ethyl ketone with 1-phenylethanethiol under the conditions described above resulted in the formation of an intractable mixture of products.

In summary, the methodology described in this work allows very easy access to 3-arylthieno[2,3-*b*]pyridines. This method has advantages over previous syntheses of thieno[2,3-*b*]pyridines because of its simplicity as well as the ready availability of the starting materials.

All melting points were obtained using a Laboratory Devices MEL-TEMP II apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal reference using a Jeol ECP500 FT NMR spectrometer operating at 500 MHz and 125 MHz, respectively. Low-resolution mass spectra (EI, 70 eV) were recorded using a Jeol JMS AX505 HA spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). The organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. *N*,*N*-Dimethylbenzamides were prepared from the respective benzoyl chlorides and dimethylamine. 2-Bromo-6-phenylpyridine (**1b**)[4] and 1-phenylethanethiol[6] were prepared according to reported procedures. All other reagents used in this study are commercially available.

(2-Bromopyridin-3-yl)(aryl)methanones 2; General Procedure

Compounds **2** were prepared by reaction of the 2-bromo-3-lithiopyridines, generated by treatment of 2-bromopyridines **1a** and **1b** with LDA according to the previously reported procedure,[5] with the respective *N*,*N*-dimethylbenzamides in THF at –78 °C. Aqueous workup (sat. aq NH_4Cl, Et_2O) followed by column chromatography on silica gel (THF–hexane) gave **2**.

(2-Bromopyridin-3-yl)(phenyl)methanone (2a)[7]

Yellow oil; R_f = 0.33 (EtOAc–hexane, 1:4).

IR (neat): 1672 cm^{-1}.

^{1}H NMR: δ = 7.42 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.50 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.63–7.68 (m, 2 H), 7.82 (d, *J* = 7.8 Hz, 2 H), 8.53 (dd, *J* = 4.6, 1.8 Hz, 1 H).

(2-Bromopyridin-3-yl)(3-methylphenyl)methanone (2b)

Yellow oil; R_f = 0.26 (THF–hexane, 1:4).

IR (neat): 1668 cm^{-1}.

^{1}H NMR: δ = 2.42 (s, 3 H), 7.38 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.42 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.46 (d, *J* = 7.3 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.65 (s, 1 H), 7.66 (dd, *J* = 7.3, 1.8 Hz, 1 H), 8.53 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.52; H, 3.71; N, 5.08.

(2-Bromopyridin-3-yl)(4-methylphenyl)methanone (2c)

Yellow oil; R_f = 0.44 (THF–hexane, 1:3).

IR (neat): 1668 cm^{-1}.

^{1}H NMR: δ = 2.44 (s, 3 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.41 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.65 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.71 (d, *J* = 7.8 Hz, 2 H), 8.51 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.31; H, 3.82; N, 5.00.

(2-Bromopyridin-3-yl)(3-chlorophenyl)methanone (2d)

Yellow oil; R_f = 0.19 (THF–hexane, 1:5).

IR (neat): 1682 cm^{-1}.

^{1}H NMR: δ = 7.43–7.46 (m, 2 H), 7.62 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.65–7.69 (m, 2 H), 7.81 (t, *J* = 1.8 Hz, 1 H), 8.55 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{12}H_7BrClNO$: C, 48.60; H, 2.38; N, 4.72. Found: C, 48.48; H, 2.49; N, 4.89.

(2-Bromopyridin-3-yl)(4-chlorophenyl)methanone (2e)[7]

Yellow solid; mp 54–56 °C (hexane–CH_2Cl_2).

IR (KBr): 1668 cm^{-1}.

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^{1}H NMR: δ = 7.34 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.43 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.48 (d, *J* = 8.7 Hz, 2 H), 7.75 (d, *J* = 8.7 Hz, 2 H), 8.54 (dd, *J* = 4.6, 1.8 Hz, 1 H).

(2-Bromo-6-phenylpyridin-3-yl)(4-methoxyphenyl)methanone (2f)
White solid; mp 105–107 °C (hexane–CH_2Cl_2).

IR (KBr): 1661 cm^{-1}.

^{1}H NMR: δ = 3.90 (s, 3 H), 6.97 (d, *J* = 9.2 Hz, 2 H), 7.46–7.52 (m, 3 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 9.2 Hz, 2 H), 8.06 (dd, *J* = 8.2, 1.4 Hz, 2 H).

Anal. Calcd for $C_{19}H_{14}BrNO_2$: C, 61.97; H, 3.83; N, 3.80. Found: C, 61.80; H, 4.02; N, 3.82.

Aryl{2-[(1-phenylethyl)sulfanyl]pyridin-3-yl]}methanones 3; General Procedure
Compounds **3** were prepared by treatment of (2-bromopyridin-3-yl)(aryl)methanones **2** with 1-phenylethanethiol[6] in DMF at r.t. in the presence of NaH. Aqueous workup (sat. aq NH_4Cl, Et_2O) followed by column chromatography on silica gel (THF–hexane) gave **3**.

Phenyl{2-[(1-phenylethyl)sulfanyl]pyridin-3-yl}methanone (3a)
Yellow oil; R_f = 0.43 (THF–hexane, 1:4).

IR (neat): 1661 cm^{-1}.

^{1}H NMR: δ = 1.70 (d, *J* = 6.9 Hz, 3 H), 5.26 (q, *J* = 6.9 Hz, 1 H), 7.06 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.18 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.25 (t, *J* = 7.3 Hz, 2 H), 7.39 (d, *J* = 7.3 Hz, 2 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.59 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.69 (dd, *J* = 7.8, 1.4 Hz, 2 H), 8.58 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39. Found: C, 74.95; H, 5.44; N, 4.38.

(3-Methylphenyl){2-[(1-phenylethyl)sulfanyl]pyridin-3-yl}methanone (3b)
Yellow oil; R_f = 0.31 (THF–hexane, 1:10).

IR (neat): 1661 cm^{-1}.

^{1}H NMR: δ = 1.70 (d, *J* = 6.9 Hz, 3 H), 2.38 (s, 3 H), 5.26 (q, *J* = 6.9 Hz, 1 H), 7.06 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.18 (td, *J* = 7.3, 0.9 Hz, 1 H), 7.25 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.31 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.39–7.40 (m, 3 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.54 (s, 1 H), 7.58 (dd, *J* = 7.3, 1.8 Hz, 1 H), 8.58 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{21}H_{19}NOS$: C, 75.64; H, 5.74; N, 4.20. Found: C, 75.40; H, 5.92; N, 4.11.

(4-Methylphenyl){2-[(1-phenylethyl)sulfanyl]pyridin-3-yl}methanone (3c)
Pale-yellow solid; mp 111–113 °C (hexane–CH_2Cl_2).

IR (KBr): 1647 cm^{-1}.

^{1}H NMR: δ = 1.69 (d, *J* = 6.9 Hz, 3 H), 2.42 (s, 3 H), 5.25 (q, *J* = 6.9 Hz, 1 H), 7.01 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 7.24 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.38 (d, *J* = 7.8 Hz, 2 H), 7.55 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 2 H), 8.57 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{21}H_{19}NOS$: C, 75.64; H, 5.74; N, 4.20. Found: C, 75.50; H, 5.92; N, 4.16.

(3-Chlorophenyl){2-[(1-phenylethyl)sulfanyl]pyridin-3-yl}methanone (3d)
Yellow oil; R_f = 0.25 (THF–hexane, 1:10).

IR (neat): 1650 cm^{-1}.

^{1}H NMR: δ = 1.71 (d, *J* = 6.9 Hz, 3 H), 5.26 (q, *J* = 6.9 Hz, 1 H), 7.08 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.26 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.36–7.40 (m, 3 H), 7.53–7.56 (m, 2 H), 7.59 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.68 (t, *J* = 1.8 Hz, 1 H), 8.60 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{20}H_{16}ClNOS$: C, 67.88; H, 4.56; N, 3.96. Found: C, 67.79; H, 4.65; N, 3.84.

(4-Chlorophenyl){2-[(1-phenylethyl)sulfanyl]pyridin-3-yl}methanone (3e)
Yellow solid; mp 112–114 °C (hexane–CH_2Cl_2).

IR (KBr): 1655 cm^{-1}.

^{1}H NMR: δ = 1.69 (d, *J* = 7.3 Hz, 3 H), 5.26 (q, *J* = 7.3 Hz, 1 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.25 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.37 (dd, *J* = 7.8, 1.4 Hz, 2 H), 7.38 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.39 (d, *J* = 8.2 Hz, 2 H), 7.56 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.62 (d, *J* = 8.2 Hz, 2 H), 8.59 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{20}H_{16}ClNOS$: C, 67.88; H, 4.56; N, 3.96. Found: C, 67.85; H, 4.50; N, 3.91.

(4-Methoxyphenyl){6-phenyl-[2-(1-phenylethyl)sulfanyl]pyridin-3-yl}methanone (3f)
White solid; mp 94–96 °C (hexane–Et_2O).

IR (KBr): 1651 cm^{-1}.

^{1}H NMR: δ = 1.77 (d, *J* = 6.9 Hz, 3 H), 3.89 (s, 3 H), 5.39 (q, *J* = 6.9 Hz, 1 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.25 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.47–7.53 (m, 6 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.76 (d, *J* = 8.7 Hz, 2 H), 8.06 (dd, *J* = 7.8, 1.4 Hz, 1 H).

Anal. Calcd for $C_{27}H_{23}NO_2S$: C, 76.21; H, 5.45; N, 3.29. Found: C, 75.97; H, 5.64; N, 2.99.

3-Alkenyl-2-[(1-phenylethyl)sulfanyl]pyridines 4; General Procedure
Compounds **4** were prepared by reaction of ketones **3** with methylene(triphenyl)phosphorane or ethylidene(triphenyl)phosphorane in THF at 0 °C. Aqueous workup (H_2O, Et_2O) followed by column chromatography on silica gel (THF–hexane) gave **4**.

2-[(1-phenylethyl)sulfanyl]-3-(1-phenylethenyl)pyridine (4a)
Pale-yellow oil; R_f = 0.29 (THF–hexane, 1:10).

IR (neat): 1614, 1601, 1385 cm^{-1}.

^{1}H NMR: δ = 1.63 (d, *J* = 6.9 Hz, 3 H), 5.17 (q, *J* = 6.9 Hz, 1 H), 5.27 (d, *J* = 0.9 Hz, 1 H), 5.83 (d, *J* = 0.9 Hz, 1 H), 7.00 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.15–7.27 (m, 8 H), 7.31–7.35 (m, 3 H), 8.45 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{21}H_{19}NS$: C, 79.45; H, 6.03; N, 4.41. Found: C, 79.28; H, 6.11; N, 4.20.

2-[(1-phenylethyl)sulfanyl]-3-[(1*E*/*Z*)-1-phenylprop-1-en-1-yl]pyridine (4a′)
Pale-yellow oil as a mixture of stereoisomers (*E*/*Z* = ca. 1:1); R_f = 0.56 (THF–hexane, 1:10).

IR (neat): 1599, 1387 cm^{-1}.

^{1}H NMR: δ = 1.65 (d, *J* = 6.9 Hz, 4.5 H), 1.86 (d, *J* = 6.9 Hz, 1.5 H), 5.15 (q, *J* = 6.9 Hz, 0.5 H), 5.20 (q, *J* = 6.9 Hz, 0.5 H), 5.84 (q, *J* = 6.9 Hz, 0.5 H), 6.32 (br s, 0.5 H), 6.92 (dd, *J* = 7.8, 4.6 Hz, 0.5 H), 7.02–7.38 (m, 11.5 H), 8.35 (dd, *J* = 4.6, 1.8 Hz, 0.5 H), 8.45 (br s, 0.5 H).

Anal. Calcd for $C_{22}H_{21}NS$: C, 79.72; H, 6.39; N, 4.23. Found: C, 79.62; H, 6.50; N, 4.19.

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3-[1-(3-Methylphenyl)ethenyl]-2-[(1-phenylethyl)sulfanyl]pyridine (4b)
Pale-yellow oil; R_f = 0.31 (THF–hexane, 1:20).

IR (neat): 1601, 1384 cm^{-1}.

^1H NMR: δ = 1.64 (d, *J* = 6.9 Hz, 3 H), 2.29 (s, 3 H), 5.18 (q, *J* = 6.9 Hz, 1 H), 5.25 (s, 1 H), 5.83 (s, 1 H), 6.97–7.02 (m, 3 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 7.17 (t, *J* = 7.3 Hz, 1 H), 7.23 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.31 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.35 (s, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 8.45 (dd, *J* = 5.0, 1.8 Hz, 1 H).

Anal. Calcd for $C_{22}H_{21}NS$: C, 79.72; H, 6.39; N, 4.23. Found: C, 79.63; H, 6.44; N, 4.12.

3-[1-(4-Methylphenyl)ethenyl]-2-[(1-phenylethyl)sulfanyl]pyridine (4c)
Pale-yellow oil; R_f = 0.46 (THF–hexane, 1:10).

IR (neat): 1609, 1385 cm^{-1}.

^1H NMR: δ = 1.64 (d, *J* = 6.9 Hz, 3 H), 2.33 (s, 3 H), 5.17 (q, *J* = 6.9 Hz, 1 H), 5.21 (s, 1 H), 5.80 (s, 1 H), 6.99 (dd, *J* = 7.3, 5.0 Hz, 1 H), 7.06 (d, *J* = 9.2 Hz, 2 H), 7.08 (d, *J* = 9.2 Hz, 2 H), 7.16 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.23 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.31 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 8.44 (dd, *J* = 5.0, 1.8 Hz, 1 H).

Anal. Calcd for $C_{22}H_{21}NS$: C, 79.72; H, 6.39; N, 4.23. Found: C, 79.65; H, 6.47; N, 4.04.

3-[1-(3-Chlorophenyl)ethenyl]-2-[(1-phenylethyl)sulfanyl]pyridine (4d)
Pale-yellow oil; R_f = 0.32 (THF–hexane, 1:10).

IR (neat): 1610, 1389 cm^{-1}.

^1H NMR: δ = 1.63 (d, *J* = 6.9 Hz, 3 H), 5.17 (q, *J* = 6.9 Hz, 1 H), 5.32 (s, 1 H), 5.83 (s, 1 H), 7.02 (dd, *J* = 7.3, 4.6 Hz, 1 H), 7.04 (d, *J* = 7.8 Hz, 1 H), 7.16–7.20 (m, 3 H), 7.23–7.26 (m, 3 H), 7.31–7.34 (m, 3 H), 8.46 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{21}H_{18}ClNS$: C, 71.68; H, 5.16; N, 3.98. Found: C, 71.63; H, 5.21; N, 4.11.

3-[1-(4-Chlorophenyl)ethenyl]-2-[(1-phenylethyl)sulfanyl]pyridine (4e)
Pale-yellow oil; R_f = 0.40 (THF–hexane, 1:5).

IR (neat): 1610, 1387 cm^{-1}.

^1H NMR: δ = 1.63 (d, *J* = 6.9 Hz, 3 H), 5.17 (q, *J* = 6.9 Hz, 1 H), 5.28 (s, 1 H), 5.80 (s, 1 H), 7.02 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 7.18 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.20–7.25 (m, 4 H), 7.30–7.33 (m, 3 H), 8.46 (dd, *J* = 4.6, 1.8 Hz, 1 H).

Anal. Calcd for $C_{21}H_{18}ClNS$: C, 71.68; H, 5.16; N, 3.98. Found: C, 71.57; H, 5.28; N, 3.91.

3-[(1*E*/*Z*)-1-(4-chlorophenyl)prop-1-en-1-yl]-2-[(1-phenylethyl)sulfanyl]pyridine (4e′)
Pale-yellow oil as a mixture of stereoisomers (*E*/*Z* = ca. 6:4); R_f = 0.58 (THF–hexane, 1:5).

IR (neat): 1601, 1387 cm^{-1}.

^1H NMR: δ = 1.64 (d, *J* = 6.9 Hz, 4.2 H), 1.85 (d, *J* = 6.9 Hz, 1.8 H), 5.14 (q, *J* = 6.9 Hz, 0.6 H), 5.19 (q, *J* = 6.9 Hz, 0.4 H), 5.85 (q, *J* = 6.9 Hz, 0.6 H), 6.30 (br s, 0.4 H), 6.91–6.95 (m, 1 H), 7.05 (d, *J* = 8.7 Hz, 1.2 H), 7.17–7.27 (m, 7.6 H), 7.34 (dd, *J* = 7.8, 1.4 Hz, 1.2 H), 8.37 (dd, *J* = 4.6, 1.8 Hz, 0.6 H), 8.46 (br s, 0.4 H).

Anal. Calcd for $C_{22}H_{20}ClNS$: C, 72.21; H, 5.51; N, 3.83. Found: C, 72.02; H, 5.53; N, 3.93.

3-[1-(4-Methoxyphenyl)ethenyl]-6-phenyl-2-[(1-phenylethyl)sulfanyl]pyridine (4f)
White solid; mp 118–120 °C (hexane–Et_2O).

IR (KBr): 1605, 1348 cm^{-1}.

^1H NMR: δ = 1.72 (d, *J* = 6.9 Hz, 3 H), 3.81 (s, 3 H), 5.24 (s, 1 H), 5.32 (q, *J* = 7.3 Hz, 1 H), 5.76 (d, *J* = 0.9 Hz, 1 H), 6.81 (d, *J* = 9.2 Hz, 2 H), 7.18 (d, *J* = 9.2 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.38–7.50 (m, 9 H), 8.05 (dd, *J* = 7.3, 1.4 Hz, 2 H).

Anal. Calcd for $C_{28}H_{25}NOS$: C, 79.40; H, 5.95; N, 3.31. Found: C, 79.38; H, 6.00; N, 3.10.

3-Phenylthieno[2,3-*b*]pyridine (5a); Typical Procedure
To a stirred solution of **4a** (0.19 g, 0.58 mmol) in MeCN (4 mL) at r.t. was added three portions each of $NaHCO_3$ (0.10 g, 1.2 mmol) and I_2 (0.29 g, 1.2 mmol) at 6 h intervals. The resulting mixture was stirred overnight at r.t., after which 10% aq $Na_2S_2O_3$ was added until the color due to iodine had disappeared. MeCN was evaporated and the remaining aq layer was extracted with Et_2O (2 × 15 mL). The combined extract was washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL) and then dried over anhyd K_2CO_3. After evaporation of the solvent, the residue was purified by preparative TLC on silica gel to afford **5a** as a pale-yellow viscous oil; yield: 88 mg (72%); R_f = 0.38 (THF–hexane, 1:10).

IR (neat): 1601, 1371, 1082 cm^{-1}.

^1H NMR: δ = 7.34 (dd, *J* = 8.2, 4.6 Hz, 1 H), 7.43 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.51 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.52 (s, 1 H), 7.56 (dd, *J* = 7.8, 1.4 Hz, 2 H), 8.20 (dd, *J* = 8.2, 1.8 Hz, 1 H), 8.62 (dd, *J* = 4.6, 1.8 Hz, 1 H).

^{13}C NMR: δ = 119.43, 123.36, 127.89, 128.38, 128.95, 130.50, 131.27, 135.36, 135.72, 146.75, 162.58.

MS (EI, 70 eV): *m*/*z* (%) = 211 (100) [M^+].

Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63. Found: C, 73.80; H, 4.22; N, 6.61.

2-Methyl-3-phenylthieno[2,3-*b*]pyridine (5a′)
Beige solid; mp 84–86 °C (hexane–Et_2O).

IR (KBr): 1601, 1387 cm^{-1}.

^1H NMR: δ = 2.54 (s, 3 H), 7.22 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.37 (dd, *J* = 7.8, 1.4 Hz, 2 H), 7.42 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.50 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.76 (dd, *J* = 7.8, 1.4 Hz, 1 H), 8.50 (dd, *J* = 4.6, 1.4 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 225 (100) [M^+].

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found: C, 74.54; H, 4.95; N, 6.35.

3-(3-Methylphenyl)thieno[2,3-*b*]pyridine (5b)
Pale-yellow solid; mp 49–51 °C (hexane).

IR (KBr): 1607, 1371 cm^{-1}.

^1H NMR: δ = 2.45 (s, 3 H), 7.24 (d, *J* = 7.3 Hz, 1 H), 7.34 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.37–7.41 (m, 3 H), 7.49 (s, 1 H), 8.20 (dd, *J* = 7.8, 1.8 Hz, 1 H), 8.61 (dd, *J* = 4.6, 1.8 Hz, 1 H).

^{13}C NMR: δ = 31.48, 119.36, 123.15, 125.40, 128.62, 128.79, 129.03, 130.55, 131.27, 135.23, 135.77, 138.64, 146.67, 162.50.

MS (EI, 70 eV): *m*/*z* (%) = 225 (100) [M^+].

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found: C, 74.46; H, 5.07; N, 6.19.

3-(4-Methylphenyl)thieno[2,3-*b*]pyridine (5c)
Pale-yellow solid; mp 59–62 °C (hexane).

IR (KBr): 1371, 1080 cm^{-1}.

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^{1}H NMR: δ = 2.44 (s, 3 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.33 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.45 (d, *J* = 7.8 Hz, 2 H), 7.47 (s, 1 H), 8.18 (dd, *J* = 7.8, 1.8 Hz, 1 H), 8.61 (dd, *J* = 4.6, 1.8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 225 (100) [M$^+$].

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found: C, 74.58; H, 5.17; N, 6.27.

3-(3-Chlorophenyl)thieno[2,3-*b*]pyridine (5d)
Pale-yellow solid; mp 100–101 °C (hexane).

IR (KBr): 1371, 1086 cm^{-1}.

^{1}H NMR: δ = 7.37 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.40–7.42 (m, 1 H), 7.44–7.45 (m, 2 H), 7.55 (s, 1 H), 7.56 (t, *J* = 1.4 Hz, 1 H), 8.18 (dd, *J* = 7.8, 1.8 Hz, 1 H), 8.63 (dd, *J* = 4.6, 1.8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 245 (100) [M$^+$].

Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70. Found: C, 63.28; H, 3.47; N, 5.48.

3-(4-Chlorophenyl)thieno[2,3-*b*]pyridine (5e)
White solid; mp 152–154 °C (hexane–CH_2Cl_2).

IR (KBr) 1371, 1088 cm^{-1}.

^{1}H NMR: δ = 7.36 (dd, *J* = 8.2, 4.6 Hz, 1 H), 7.48 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 7.51 (s, 1 H), 8.14 (dd, *J* = 8.2, 1.8 Hz, 1 H), 8.63 (dd, *J* = 4.6, 1.8 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 245 (100) [M$^+$].

Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70. Found: C, 63.70; H, 3.08; N, 5.59.

3-(4-Chlorophenyl)-2-methylthieno[2,3-*b*]pyridine (5e′)
Pale-yellow oil; R_f = 0.28 (THF–hexane, 1:10).

IR (neat): 1387, 1091 cm^{-1}.

^{1}H NMR: δ = 2.53 (s, 3 H), 7.24 (dd, *J* = 7.8, 4.6 Hz, 1 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 7.72 (dd, *J* = 7.8, 1.4 Hz, 1 H), 8.51 (dd, *J* = 4.6, 1.4 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 259 (100) [M$^+$].

Anal. Calcd for $C_{14}H_{10}ClNS$: C, 64.73; H, 3.88; N, 5.39. Found: C, 64.81; H, 4.02; N, 5.21.

3-(4-Methoxyphenyl)-6-phenylthieno[2,3-*b*]pyridine (5f)
White solid; mp 97–99 °C (hexane–Et_2O).

IR (KBr): 1611, 1361, 1076 cm^{-1}.

^{1}H NMR: δ = 3.88 (s, 3 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 7.41 (s, 1 H), 7.43 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.49–7.52 (m, 4 H), 7.77 (d, *J* = 8.7 Hz, 1 H), 8.11 (dd, *J* = 7.3, 1.4 Hz, 2 H), 8.20 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR: δ = 55.38, 114.38, 116.78, 122.38, 127.23, 128.00, 128.80, 129.00, 129.44, 130.03, 131.01, 135.19, 139.11, 154.63, 159.38, 162.85.

Anal. Calcd for $C_{20}H_{15}NOS$: C, 75.68; H, 4.76; N, 4.41. Found: C, 75.51; H, 4.99; N, 4.27.

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References

(1) Kobayashi, K.; Nakamura, D.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1780.
(2) (a) Patel, M. V.; Rohde, J. J.; Gracias, V.; Kolasa, T. *Tetrahedron Lett.* **2003**, *44*, 6665. (b) Parnes, J. S.; Delgado, M. *Heterocycles* **2004**, *63*, 2199. (c) Abdelhamid, A.; Al-Atoom, A. *Synth. Commun.* **2006**, *36*, 97. (d) Nurkkala, L. J.; Steen, R. O.; Dunne, S. I. *Synthesis* **2006**, 1295.
(3) (a) Bernardino, A. M. R.; Pinheiro, L. C. S.; Carneiro, J. W. D.; Ferreira, V. F.; Azevedo, A. R.; Souza, T. M. L.; Frugulhetti, I. C. C. P. *Heterocycl. Commun.* **2004**, *10*, 407. (b) Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3411. (c) Boshelli, D. H.; Wu, B.; Sosa, A. C. B.; Durutlic, H.; Ye, F.; Ranfield, Y.; Golas, J. M.; Boschelli, F. *J. Med. Chem.* **2004**, *47*, 6666. (d) Moretto, A. F.; Kirincich, S. J.; Xu, W. X.; Smith, M. J.; Wan, Z.-K.; Wilson, D. P.; Follows, B. C.; Binnun, E.; Joseph-McCarthy, D.; Foreman, K.; Erbe, D. V.; Zhang, Y. L.; Tam, S. K.; Tam, S. Y.; Lee, J. *Bioorg. Med. Chem.* **2006**, *14*, 2162. (e) Morwick, T.; Berry, A.; Brickwood, J.; Cardozo, M.; Catron, K.; DeTuri, M.; Emeigh, J.; Homon, C.; Hrapchak, M.; Jacober, S.; Jakes, S.; Kaplita, P.; Kelly, T. A.; Ksiazek, J.; Liuzzi, M.; Magolda, R.; Mao, C.; Marshall, D.; McNeil, D.; Prokopowicz, A. III; Sarko, C.; Scouten, E.; Sledziona, C.; Sun, S.; Watrous, J.; Wu, J. P.; Cywin, C. L. *J. Med. Chem.* **2006**, *49*, 2898. (f) Bernardino, A. M. R.; da Silva Pinheiro, L. C.; Rodrigues, C. R.; Loureiro, N. I.; Castro, H. C.; Lanfredi-Rangel, A.; Sabatini-Lopes, J.; Borges, J. C.; Carvalho, J. M.; Romerio, G. A.; Ferreira, V. F.; Frugulhetti, I. C. P. P.; Vannier-Santos, M. A. *Bioorg. Med. Chem.* **2006**, *14*, 5765. (g) Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Prajapati, V. M.; Patel, D. N.; Gupta, A. A.; Sharma, A.; Tom, R.; Bandyopadhya, D.; Modi, H.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 6782. (h) Al-Omran, F. A.; El-Khair, A. A. *J. Heterocycl. Chem.* **2008**, *45*, 1057. (i) Boschelli, D. H.; Wu, B.; Sosa, A. C. B.; Chen, J.; Asselin, M.; Cole, D. C.; Lee, J.; Yang, X.; Chaudhary, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2850. (j) Leal, B.; Afonso, I. F.; Rodorigues, C. R.; Abreu, P. A.; Garrett, R.; Pinheiro, L. C. S.; Azevedo, A. R.; Borges, J. C.; Vegi, P. F.; Santos, C. C. C.; da Silveira, F. C. A.; Cabral, L. M.; Frugulhetti, I. C. P. P.; Bernardino, A. M. R.; Santos, D. O.; Castro, H. C. *Bioorg. Med. Chem.* **2008**, *16*, 8196.
(4) Vandromme, L.; Reiβig, H.-U.; Gröper, S.; Rabe, J. P. *Eur. J. Org. Chem.* **2008**, 2049.
(5) Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R. *Synthesis* **2005**, 330.
(6) Kellogg, R. M.; Nieuwenhuijzen, J. W.; Vries, T. R.; Broxterman, Q. B.; Grimbergen, R. F. P.; Kaptein, B.; La Crois, R. M.; de Wever, E.; Zwaagstra, K.; van der Laan, A. C. *Synthesis* **2003**, 1626.
(7) Marsais, F.; Laperdrix, B.; Guengoer, T.; Mallet, M.; Queguiner, G. *J. Chem. Res., Synop.* **1982**, 278.

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