We have recently reported the synthesis of 3-substituted benzo[b]thiophenes, 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 from readily available 2-bromopyridines, which is based on the reaction of 3-(1-arylalkenyl)-2-[(1-phenylethyl)sulfanyl]pyridines with iodine. Several methods have been reported for the preparation of thieno[2,3-b]pyridines, as many derivatives possessing this skeleton have been reported to exhibit varied biological activity. 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. 2-Bromopyridines 1a and 1b were first lithiated using lithium diisopropylamide (LDA) in tetrahydrofuran at –78 °C, via the reported procedure, to afford the corresponding 2-bromo-3-lithiopyridines. These were then reacted with various N,N-dimethylbenzamides to give 3-aroyl-2-bromopyridines in good yields. Next, the 2-bromo group was substituted with a (1-phenylethyl)sulfanyl group by reaction with 1-phenylethanethiol and sodium hydride in N,N-dimethylformamide at room temperature to afford aryl 2-[(1-phenylethyl)sulfanyl]pyridin-3-yl ketones in good yields, as illustrated in Table 1.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>Yield (%) of 2</th>
<th>Yield (%) of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>Ph</td>
<td>54</td>
<td>87</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>3-MeC6H4</td>
<td>56</td>
<td>79</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>4-MeC6H4</td>
<td>58</td>
<td>81</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>3-CIC6H4</td>
<td>52</td>
<td>78</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>4-CIC6H4</td>
<td>63</td>
<td>76</td>
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<tr>
<td>f</td>
<td>Ph</td>
<td>4-MeOC6H4</td>
<td>61</td>
<td>86</td>
</tr>
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</table>

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 methyl(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. 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-
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.

In summary, the methodology described in this work allowed the conditions described above resulted in the preparation of 3-ethylthieno[2,3-b]pyridine with 1-phenylethanethiol unreacted using the present method. The reaction of 2-bromo-6-phenylpyridine (1b) and 1-phenylethanethiol 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, with the respective N,N-dimethylbenzamides in THF at –78 °C. Aqueous workup (sat. aq NH4Cl, Et2O) followed by column chromatography on silica gel (THF–hexane) gave 2.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R^2</th>
<th>Yield (%)(^{a}) of 4</th>
<th>Yield (%)(^{a}) of 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>H</td>
<td>4a (89)</td>
<td>5a (72)</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>Me</td>
<td>4a’ (75)</td>
<td>5a’ (40)</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>H</td>
<td>4b (87)</td>
<td>5b (75)</td>
</tr>
<tr>
<td>4</td>
<td>3c</td>
<td>H</td>
<td>4c (93)</td>
<td>5c (70)</td>
</tr>
<tr>
<td>5</td>
<td>3d</td>
<td>H</td>
<td>4d (86)</td>
<td>5d (76)</td>
</tr>
<tr>
<td>6</td>
<td>3e</td>
<td>H</td>
<td>4e (91)</td>
<td>5e (67)</td>
</tr>
<tr>
<td>7</td>
<td>3e</td>
<td>Me</td>
<td>4e’ (84)</td>
<td>5e’ (33)</td>
</tr>
<tr>
<td>8</td>
<td>3f</td>
<td>H</td>
<td>4f (86)</td>
<td>5f (72)</td>
</tr>
</tbody>
</table>

\(^{a}\) 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-phenylethanol 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) and 1-phenylethanethiol were prepared according to reported procedures. All other reagents used in this study are commercially available.

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

**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, with the respective N,N-dimethylbenzamides in THF at –78 °C. Aqueous workup (sat. aq NH\(_4\)Cl, Et\(_2\)O) followed by column chromatography on silica gel (THF–hexane) gave 2.

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

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<tr>
<td>3</td>
<td>3b</td>
<td>H</td>
<td>4b (87)</td>
<td>5b (75)</td>
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<tr>
<td>4</td>
<td>3c</td>
<td>H</td>
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<td>5</td>
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<td>3f</td>
<td>H</td>
<td>4f (86)</td>
<td>5f (72)</td>
</tr>
</tbody>
</table>

\(^{a}\) Yield of isolated product.
(2-Benzyl-3-(phenylsulfanyl)pyridin-3-yl)(4-methoxyphenyl)methanone
(2f)
White solid; mp 105–107 °C (hexane–CH₂Cl₂).

IR (KBr): 1661 cm⁻¹.

¹H 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).

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

IR (neat): 1650 cm⁻¹.

¹H NMR: δ = 1.19 (dd, 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).


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\(^{-1}\).

3-[1-(4-Methylphenyl)ethenyl]-2-[(1-phenylethyl)sulfanyl]pyridine (5a)
Beige solid; mp 84–86 °C (hexane–Et\(_2\)O).

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

3-[1-(4-Methylphenyl)ethenyl]-6-phenyl-2-[(1-phenylethyl)sulfanyl]pyridine (5b)
Pale-yellow solid; mp 59–62 °C (hexane).

IR (KBr): 1371, 1080 cm\(^{-1}\).
3-(4-Chlorophenyl)thieno[2,3-b]pyridine (5d)

Pale-yellow solid; mp 97–99 °C (hexane–Et2O).

MS (EI, 70 eV):

1H NMR: δ = 8.7 (s, 1 H), 7.49 (d, J = 7.8, 1 H), 7.40–7.42 (m, 1 H), 7.72 (d, J = 8.7, 1 H), 8.63 (dd, J = 4.6, 1.8 Hz, 1 H).

IR (KBr): 1371, 1086 cm–1.

Anal. Calcd for C14H10ClNS: C, 64.73; H, 3.88; N, 5.39. Found: C, 64.81; H, 4.02; N, 5.39.

Acknowledgment

We are much indebted to Mrs. Miyuki Tanmatsu of Tottori University for her contributions to determining mass spectra and performing combustion analyses.

References


