The Synthesis of Thieno[2,3-b]pyridine Derivatives

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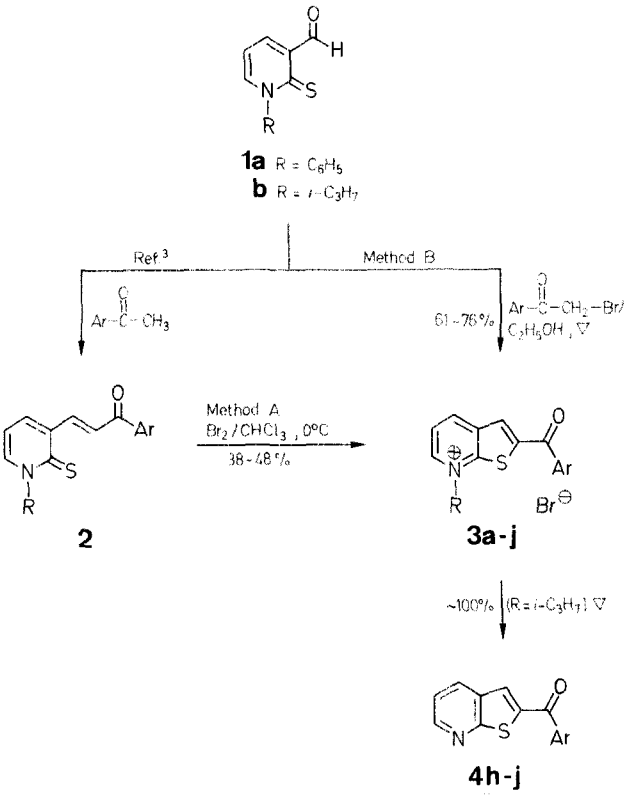
Thieno[2,3-*b*]pyridine derivatives **3** are prepared either by the reaction of pyridine-2-thiones **1** with phenacyl bromides or by bromination of vinyl ketones **2**.

Several methods have been adopted for the synthesis of thieno[2,3-*b*]pyridine derivatives and have been comprehensively reviewed[1,2,3]. The methods can be classified into two groups. The first one involves formation of the pyridine ring starting from aminothiophenes or *o*-aminocarbonylthiophenes; however, the inaccessibility of these derivatives is a considerable practical problem. The second method involves formation of the thiophene ring by cyclization of carboxypyridylthioacetic or cyanopyridylacetic acid derivatives.

We now report an apparently widely applicable synthesis of the unknown *N*-substituted thieno[2,3-b]pyridinium system **3** by two approaches. The first one involves bromination of the vinyl ketones **2**, readily available[4] from 1-aryl- or 1-alkyl-3-formyl-2(1*H*)-pyridinethiones (**1a** and **1b**, respectively) (Method A). The second method is based on the reaction of compounds **1** with phenacyl bromides (Method B).



3	R	Ar	3	R	Ar
a			f		O_2N
b		H_3C	g		
c		H_3CO	h	i-C_3H_7	
d		Cl	i	i-C_3H_7	Br
e		Br	j	i-C_3H_7	Cl

We believe that the conversion **2** → **3** (Method A) must follow the mechanism suggested[5] for the reaction of 1-alkenyl-2(1*H*)-pyridinethiones with bromine which involves addition of the halogen to the activated vinyl ketone double bond, followed by intramolecular alkylation of sulfur and finally elimination of hydrogen bromide, whereas the conversion **1** → **3** (Method B) involves *S*-alkylation followed by cyclocondensation.

It is well known[6] that 1-substituted 4,6-diphenyl-2-methylthiopyridinium iodides yield 4,6-diphenyl-2-methylthiopyridine upon thermolysis. We consequently tested the expected reactivity of **3** and the good leaving group ability of the thieno[2,3-*b*]pyridine ring system. Thus, heating compounds **3h–3j** at a temperature slightly above their melting points (220–250 °C) for a short time gave the corresponding thieno[2,3-*b*]pyridines **4** in nearly quantitative yields. One of us[7] has briefly mentioned the preparation of a few 2-acylthieno[2,3-*b*]pyridines from parent 3-formyl-2(1*H*)-pyridinethione (**1**; R = H); however, the method described here is more versatile as the condensation products **2** can be easily prepared from acetophenones.

Table. Thieno[2,3-*b*]pyridine Derivatives **3** and **4** prepared

Product	Yield[a] [%] (Method)	m.p.[b] [°C]	Molecular Formula[c] or Lit. m.p. [°C]	I.R. (Nujol)[d] $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R.[e] δ [ppm]	M.S. (70 eV)[f] *m/e* (rel. int. %)
3a	66 (B)	303–305°	$C_{20}H_{14}BrNOS$ (396.3)	1631	9.9–9.5 (m, 2H); 8.90 (s, 1H); 8.60 (dd, J = 6 Hz, 8 Hz, 1H); 8.4–7.6 (m, 10H)	317 (45), 316 (100), 301 (49), 212 (12), 105 (16), 77 (10)
3b	47 (A)	250–252°	$C_{21}H_{16}BrNOS$ (410.3)	1631	9.8–9.4 (m, 2H); 8.80 (s, 1H); 8.50 (dd, J = 6 Hz, 8 Hz, 1H); 8.3–7.5 (m, 9H); 2.50 (s, 3H)	330 (100), 329 (5), 212 (5), 119 (10), 91 (10), 77 (7)
3c	48 (A)	248–250°	$C_{21}H_{16}BrNO_2S$ (426.3)	1619	9.8–9.4 (m, 2H); 8.80 (s, 1H); 8.45 (dd, J = 6 Hz, 8 Hz, 1H); 8.3–7.2 (m, 9H); 4.00 (s, 3H)	346 (100), 316 (5), 212 (9), 211 (7), 135 (14), 77 (10)
3d	38 (A)	303–304°	$C_{20}H_{13}BrClNOS$ (430.7)	1631	9.9–9.5 (m, 2H); 8.80 (s, 1H); 8.55 (dd, J = 6 Hz, 8 Hz, 1H); 8.3–7.7 (m, 9H)	352 (40), 350 (100), 212 (8), 139 (9), 111 (5), 77 (8)
3e	74 (B)	253–255°	$C_{20}H_{13}Br_2NOS$ (475.2)	1630	9.8–9.5 (m, 2H); 8.90 (s, 1H); 8.50 (dd, J = 6 Hz, 8 Hz, 1H); 8.3–7.8 (m, 9H)	397 (27), 396 (100), 212 (14), 185 (10), 155 (5), 77 (16)
3f	61 (B)	316–318°	$C_{20}H_{13}BrN_2O_3S$ (441.3)	1653	9.8–9.5 (m, 2H); 8.90 (s, 1H); 8.7–7.9 (m, 10H)	362 (27), 361 (100), 316 (10), 315 (23), 212 (11), 185 (10), 77 (12)
3g	64 (B)	287–290°	$C_{26}H_{18}BrNOS$ (472.4)	1625	9.8–9.5 (m, 2H); 8.95 (s, 1H); 8.55 (dd, J = 6 Hz, 8 Hz, 1H); 8.4–7.5 (m, 14H)	394 (14), 393 (34), 392 (100), 212 (18), 181 (12), 152 (12), 77 (16)
3h	73 (B)	213–214°	$C_{17}H_{16}BrNOS$ (362.3)	1636	9.75 (dd, J = 2 Hz, 6 Hz, 1H); 9.35 (dd, J = 2 Hz, 8 Hz, 1H); 8.75 (s, 1H); 8.35 (dd, J = 6 Hz, 8 Hz, 1H); 8.3–7.5 (m, 5H); 5.40 (sept, J = 7 Hz, 1H); 1.85 (d, J = 7 Hz, 6H)	284 (12), 283 (28), 282 (100), 240 (30), 105 (18), 77 (6), 43 (5)
3i	67 (B)	245–247°	$C_{17}H_{15}Br_2NOS$ (441.2)	1642	10.25 (dd, J = 2 Hz, 6 Hz, 1H); 9.65 (dd, J = 2 Hz, 8 Hz, 1H); 9.00 (s, 1H); 8.60 (dd, J = 6 Hz, 8 Hz, 1H); 8.25 (s, 4H); 5.50 (sept, J = 7 Hz, 1H); 1.85 (d, J = 7 Hz, 6H)	363 (30), 362 (100), 318 (22), 183 (16), 162 (8), 135 (11), 43 (11)
3j	76 (B)	238–240°	$C_{17}H_{15}BrClNOS$ (396.7)	1648	10.05 (dd, J = 2 Hz, 6 Hz, 1H); 9.65 (dd, J = 2 Hz, 8 Hz, 1H); 9.00 (s, 1H); 8.60 (dd, J = 6 Hz, 8 Hz, 1H); 8.4–7.9 (m, 4H); 5.50 (sept, J = 7 Hz, 1H); 1.80 (d, J = 7 Hz, 6H)	319 (14), 318 (43), 316 (100), 276 (10), 274 (25), 139 (21), 135 (7), 43 (7)
4h	91	97–99°	96–98[8]	1631	9.10 (dd, J = 2 Hz, 4 Hz, 1H); 8.80 (dd, J = 2 Hz, 8 Hz, 1H); 8.45 (s, 1H); 8.3–7.7 (m, 5H)	239 (94), 211 (14), 162 (78), 134 (24), 105 (100), 90 (16), 77 (85)
4i	92	179–180°	180–181[8]	1625	8.95 (dd, J = 2 Hz, 5 Hz, 1H); 8.65 (dd, J = 2 Hz, 8 Hz, 1H); 8.30 (s, 1H); 8.2–7.6 (m, 5H)	319 (100), 317 (95), 238 (23), 185 (53), 183 (55), 157 (25), 155 (24)
4j	92	176–178°	$C_{14}H_8ClNOS$ (273.7)	1636	9.00 (dd, J = 2 Hz, 5 Hz, 1H); 8.65 (dd, J = 2 Hz, 8 Hz, 1H); 8.30 (s, 1H); 8.2–7.6 (m, 5H)	275 (38), 274 (17), 273 (100), 238 (13), 162 (15), 139 (7)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] The microanalyses were in good agreement with the calculated values (C ±0.14, H ±0.15, N ±0.16).
[d] Recorded on a Nicolet FT 5DX spectrometer.
[e] Recorded at 60 MHz on a Varian EM-360A spectrometer, in DMSO-d_6 with TMS as internal standard.
[f] For compounds **3** obtained on a Varian Mat 311 A spectrometer by the F. A. B. technique and the isotopic patterns of the molecular ions are in accordance with the elemental composition in all cases. For compounds **4** obtained on a Hewlett-Packard 5993C.

Structures of the new thieno[2,3-*b*]pyridinium bromides **3** are based on microanalytical data and spectral evidence. In the I. R. spectra the compounds show absorption band for the carbonyl group at 1653–1619 cm^{-1}. The F.A.B. (Fast Atom Bombardment) mass spectra of all compounds **3** show the expected fragment ion $[M^+—Br]$ as the base peak, showing furthermore a relatively large peak arising from the $Ar—CO^+$ fragment ion. Salient features of the ^{1}H-N.M.R. spectra are given in the Table.

Vinyl Ketones 2:

The following unreported vinyl ketones **2** are prepared according to the procedure previously described[3] from aryl methyl ketones and 1-phenyl-3-formyl-2(1*H*)-pyridinethione.

3-[2-(4-Methylbenzoyl)vinyl]-1-phenyl-2(1H)-pyridinethione
(**2**; Ar = 4-$H_3C—C_6H_4$); yield: 65%; yellow crystals; m.p. 145°C.

$C_{21}H_{17}NOS$	calc.	C 76.10	H 5.17	N 4.23
(331.42)	found	76.21	5.19	4.08

3-[2-(4-Methoxybenzoyl)vinyl]-1-phenyl-2(1H)-pyridinethione
(**2**; Ar = 4-$H_3CO—C_6H_4$); yield: 72%; yellow crystals; m.p. 170–172°C.

$C_{21}H_{17}NO_2S$	calc.	C 72.59	H 4.93	N 4.03
(347.44)	found	72.65	5.08	4.19

3-[2-(4-Bromobenzoyl)vinyl]-1-phenyl-2(1H)-pyridinethione
(**2**; Ar = 4-Br—C_6H_4); yield: 81%; yellow crystals; m.p. 168–170°C.

$C_{20}H_{14}BrNOS$	calc.	C 60.61	H 3.56	N 3.53
(396.31)	found	60.48	3.51	3.62

2-Aroyl-7-substituted-thieno[2,3-*b*]pyridinium Bromides 3; General Procedure.

Method A: A solution of bromine (0.48 g, 3 mmol) in chloroform (20 ml) is added dropwise to a well stirred solution of the appropriate vinyl ketone **2** (3 mmol) in the same solvent (25 ml) at 0°C. When the addition has been completed the solvent is removed under reduced pressure and the solid residue is recrystallized from ethanol to give **3** as crystalline solids (Table).

Method B: To a solution of 3-formyl-1-substituted-2(1*H*)-pyridinethione **1** (3 mmol) in anhydrous ethanol (25 ml) the appropriate phenacyl bromide (3 mmol) is added. The reaction mixture is stirred at reflux temperature for 15 h. After cooling, the precipitated solid is separated by filtration, dried and recrystallized from ethanol to give **3** (Table).

2-Aroyl-thieno[2,3-*b*]pyridines 4; General Procedure.

The 2-aroyl-7-isopropyl-thieno[2,3-b]pyridinium bromide **3** is dried at 60°C/1 torr for 5 h and is then heated at a temperature slightly above its melting point (220–250°C) under reduced pressure (1 torr) for 15 min. After cooling, the solid residue is recrystallized from ethanol to give **4** in almost quantitative yield (Table).

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