A Facile and Concise Synthesis of 2-Alkyl- and 2-Aryl-4-oxo-4*H*-thiopyrano[2,3-*b*]pyridines

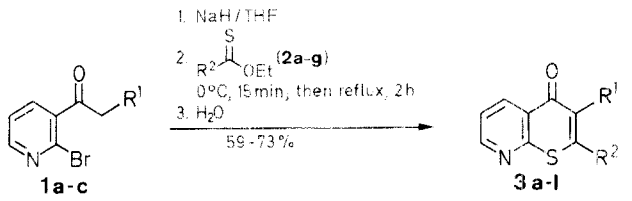
Axel Couture,* Pierre Grandclaudon, Eric Huguerre

Laboratoire de Chimie Organique Physique, U.A. C.N.R.S. N° 351, Université des Sciences & Techniques de Lille Flandres Artois, F-59655 Villeneuve d'Ascq Cedex, France

2-Alkyl- and 2-aryl-4-oxo-4*H*-thiopyrano[2,3-*b*]pyridine can be conveniently prepared by reacting the appropriate aromatic and aliphatic *O*-ethyl thiocarboxylates with the sodium derivative of various alkyl 3-(2-bromopyridyl) ketones.

Although a plethora of synthetic methods for the elaboration of fused polyheterocycles has been developed in the recent years, a certain number of these systems still remain barely accessible. This is particularly the case of 2-alkyl- and 2-aryl-4-oxo-4*H*-thiopyrano[2,3-*b*]pyridine **3** which can be regarded as the aza-analogs of thioflavones. It was firstly demonstrated that the methodology devised for the synthesis of azaflavone was not transposable to the corresponding thio-derivatives.[1] Recently a new synthetic route to these heterobicyclic systems has been developed which recommends the treatment of 2-chloro-3-ethoxycarbonylpyridine with sodium *tert*-butanethiolate followed by Claisen condensation with ketones and ultimate ring closure of the β-diketone with concentrated hydrochloric acid.[2] However, the overall yield of this multistep reaction does not exceed a 13% yield, calculated from 2-chloro-3-ethoxycarbonylpyridine, and the method is rather restrictive, especially with regard to the substituents R^1 and R^2 in **1**. We therefore directed our investigations towards a novel, general, and effective synthetic approach to these fused heterocyclic systems.

Our strategy consists in reacting aliphatic and aromatic thiocarboxylates **2a–g** with the anion of various alkyl 3-(2-bromopyridyl) ketones **1a–c**.



1–3	R^1	R^2	1–3	R^1	R^2
a	H	Et	**g**	H	2-thienyl
b	H	4-$CH_3C_6H_4$	**h**	CH_3	4-ClC_6H_4
c	H	4-$MeOC_6H_4$	**i**	CH_3	CH_3
d	H	4-ClC_6H_4	**j**	CH_3	2-furyl
e	H	CH_3	**k**	Et	Ph
f	H	2-furyl	**l**	Et	2-furyl

The *O*-ethyl thiocarboxylates **2a–g** are efficiently prepared by a conventional method: treatment of aromatic, heteroaromatic, and aliphatic carboximidic acid esters, readily accessible from the appropriate nitriles via the Pinner reaction, with hydrogen sulfide at low temperature.[3]

The alkyl 3-(2-bromopyridyl) ketones **1a–c** are synthesized by oxidation with chromium(VI) oxide[4] of the corresponding alcohols obtained by quenching the 2-bromo-3-lithiopyridine with the appropriate aldehydes[5] (Table 1).

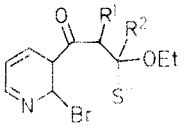
Table 1. Alkyl 3-(2-Bromopyridyl) Ketones **1a–c** Prepared

Product	Yield (%)[a]	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c,d] δ, *J*(Hz)
1a	47	C_7H_6BrNO (200.0)	2.6 (s, 3H, CH_3); 7.2–7.4 (m, 1H, H_{pyr}); 7.6 (dd, *J* = 7.5, 2.0, 1H, H_{pyr}); 8.4 (dd, *J* = 4.6, 2.0, 1H, H_{pyr})
1b	47	C_8H_8BrNO (214.1)	1.2 (t, *J* = 7.4, 3H, CH_3); 2.9 (q, *J* = 7.4, 2H, CH_2); 7.2–7.4 (m, 1H, H_{pyr}); 7.6 (dd, *J* = 7.5, 2.0, 1H, H_{pyr}); 8.4 (dd, *J* = 4.8, 2.0, 1H, H_{pyr})
1c	46	$C_9H_{10}BrNO$ (228.1)	1.0 (t, *J* = 6.8, 3H, CH_3); 1.4–1.9 (m, 2H, CH_2); 2.9 (t, *J* = 6.9, 2H, CH_2); 7.2–7.5 (m, 1H, H_{pyr}); 7.6 (dd, *J* = 7.5, 2.1, 1H, H_{pyr}); 8.4 (dd, *J* = 4.6, 2.1, 1H, H_{pyr})

[a] Overall yield based on 2-bromopyridine.
[b] Satisfactory microanalyses obtained: C ±0.19, H ±0.25, N ±0.29.
[c] IR (neat): ν = 1690–1695 cm^{-1} (C=O).
[d] Recorded on a Bruker WP 60 spectrometer.

The anion of the 3-(2-bromopyridyl) methyl and ethyl ketones **(1a, b)** is generated with sodium hydride in tetrahydrofuran at low temperature. The cyclocondensation which gives rise to the fused polyheterocycles **3a–j** is induced by refluxing a mixture of the resulting anion with the thiocarboxylates **2a–g** in tetrahydrofuran. The 2-alkyl- and 2-aryl-4-oxo-4*H*-thiopyrano[2,3-*b*]pyridines **3a–j** are then obtained with fairly good yields by this method (Table 2).

It should be noted that the preparation of the 2-aryl-3-ethyl-4*H*-thiopyrano[2,3-*b*]pyridines **3k, l** by condensation of the anion of the 3-(2-bromopyridyl) ethyl ketone **(1c)** with the suitable thiocarboxylates **2a, f** requires higher temperature, as the reactions must be carried out at 140°C in *N*-methyl-2-pyrrolidone.



4

It is likely that these reactions proceed via the intermediacy of a species like **4**. Moreover the intramolecular cyclization takes advantage of the great nucleophilicity of the transient sulfur anion and of the remarkable sensitivity of the bromine atom in α-bromopyridines with respect to nucleophilic attacks.

The reactions reported here therefore represent a new and efficient method for the synthesis of the hardly attainable 4-oxo-4*H*-thiopyrano[2,3-*b*]pyridines. On the other hand they significantly broaden the synthetic utility of aromatic and aliphatic thiocarboxylates in the elaboration of polyheterocyclic frameworks.[6]

Preparation of the Starting Materials

Aromatic and Aliphatic O-Ethyl Thiocarboxylates: The thiocarboxylates **2a–g** are prepared by treatment of the corresponding carboximidic acid esters with H_2S. Initially, aromatic and aliphatic nitriles (0.15 mol) are converted to the salts of their carboximidic acid esters by treatment with EtOH (2 equiv) and HCl (0.19 mol) in $CHCl_3$ (30 mL) at 0°C.[3] After 5 days in the refrigerator, these salts are treated with NH_3 which gives rise to the desired carboximidates; yield: 77–90%.

The thiocarboxylates **2a–g** are prepared in the following manner: dried cation exchange resin (Dowex® 50W-X8, H^+, 16 g, 80 mmol) is added to a solution of the appropriate carboximidic acid ester (50 mmol) in dry MeOH (200 mL). The mixture is stirred rapidly and cooled to −30°C in an acetone/dry ice slush bath. Then H_2S gas is passed through the

Table 2. 4-Oxo-4*H*-thiopyrano[2,3-*b*]pyridines **3a–l** Prepared

Product	Yield (%)	mp[a] (°C)	Molecular Formula[b] or Lit. mp (°C)	MS (70 eV)[c] *m/z*	^{1}H-NMR ($CDCl_3$/TMS)[d,e] δ, *J* (Hz)
3a	70	118–119	113–116[2]	239 (M^+, 100); 211 (50); 137 (30); 109 (90)	7.2 (s, 1H, H-3); 7.5–7.7 (m, 6H, H_{Ph} + H_{pyr}); 8.6–8.8 (m, 2H, H_{pyr})[f]
3b	71	157–158	$C_{15}H_{11}NOS$ (253.3)	253 (M^+, 100); 225 (45); 137 (10); 109 (20)	2.4 (s, 3H, CH_3); 7.2 (s, 1H, H-3); 7.3 (d, *J* = 8.3, 2H, H_{Ph}); 7.4 (m, 1H, H_{pyr}); 7.6 (d, *J* = 8.3, 2H, H_{Ph}); 8.6–8.8 (m, 2H, H_{pyr})
3c	73	155–156	150–151[2]	269 (M^+, 100); 241 (50); 137 (25); 109 (70)	3.8 (s, 3H, OCH_3); 7.0 (d, *J* = 9.0, 2H, H_{Ph}); 7.2 (s, 1H, H-3); 7.4–7.5 (m, 1H, H_{pyr}); 7.6 (d, *J* = 9.0, 2H, H_{Ph}); 8.6–8.8 (m, 2H, H_{pyr})
3d	66	203–204	$C_{14}H_8ClNOS$ (273.7)	275 (M^+, 35); 273 (M^+, 100); 247 (23); 245 (62); 137 (30); 109 (50)	7.2 (s, 1H, H-3); 7.5–7.7 (m, 5H, H_{pyr} + H_{Ph}); 8.6–8.8 (m, 2H, H_{pyr})
3e	63	156–157	C_9H_7NOS (177.2)	177 (M^+, 100); 149 (30); 137 (20); 109 (35)	2.4 (d, *J* = 1.1, 3H, CH_3); 6.8 (d, *J* = 1.1, 1H, H-3); 7.3–7.5 (m, 1H, H_{pyr}); 8.6–8.8 (m, 2H, H_{pyr})
3f	65	209–210	$C_{12}H_7NO_2S$ (229.3)	229 (M^+, 100); 201 (40); 137 (10); 109 (25)	6.5 (dd, *J* = 3.6, 1.8, 1H, H_{furan}); 7.0 (d, *J* = 3.6, 1H, H_{furan}); 7.3 (s, 1H, H-3); 7.4–7.5 (m, 1H, H_{pyr}); 7.6 (d, *J* = 1.8, 1H, H_{furan}); 8.6–8.8 (m, 2H, H_{pyr})
3g	69	194–195	$C_{12}H_7NOS_2$ (245.3)	245 (M^+, 100); 217 (50); 137 (10); 109 (30)	7.2 (s, 1H, H-3); 7.3–7.6 (m, 4H, H_{pyr} + $H_{thiophene}$); 8.6–8.8 (m, 2H, H_{pyr})
3h	70	137–138	$C_{15}H_{10}ClNOS$ (287.8)	289 (M^+, 20); 287 (M^+, 60); 252 (50)	2.1 (s, 3H, CH_3); 7.5–7.7 (m, 5H, H_{Ph} + H_{pyr}); 8.6–8.8 (m, 2H, H_{pyr})
3i	68	138–140	$C_{10}H_9NOS$ (191.2)	191 (M^+, 100); 162 (16); 158 (32)	2.1 (s, 3H, CH_3); 2.4 (s, 3H, CH_3); 7.3–7.5 (m, 1H, H_{pyr}); 8.6–8.8 (m, 2H, H_{pyr})
3j	61	136–138	$C_{13}H_9NO_2S$ (243.3)	243 (M^+, 100); 214 (52); 186 (23)	2.4 (s, 3H, CH_3); 6.5 (dd, *J* = 3.6, 1.8, 1H, H_{furan}); 7.0 (d, *J* = 3.6, 1H, H_{furan}); 7.4–7.5 (m, 1H, H_{pyr}); 7.6 (d, *J* = 1.8, 1H, H_{furan}); 8.6–8.8 (m, 2H, H_{pyr})
3k	60	104–106	$C_{16}H_{13}NOS$ (267.3)	267 (M^+, 50); 266 (70); 186 (91); 184 (100)	1.0 (t, *J* = 7.3, 3H, CH_3); 2.5 (q, *J* = 7.3, 2H, CH_2); 7.4 (m, 6H, H_{Ph} + H_{pyr}); 8.7–8.8 (m, 2H, H_{pyr})
3l	59	120–122	$C_{14}H_{11}NO_2S$ (257.3)	257 (M^+, 100); 256 (50); 229 (32); 228 (52); 214 (60); 203 (74)	1.2 (t, *J* = 7.3, 3H, CH_3); 2.9 (q, *J* = 7.3, 2H, CH_2); 6.5 (dd, *J* = 3.5, 1.8, 1H, H_{furan}); 6.9 (d, *J* = 3.5, 1H, H_{furan}); 7.2–7.6 (m, 2H, H_{pyr} + H_{furan}); 8.6–8.8 (m, 2H, H_{pyr})

[a] Uncorrected, measured with a Reichert-Termopan apparatus; recrystallized from hexane/toluene (except for **3k, l**).

[b] Satisfactory microanalyses obtained: C ±0.28, H ±0.25, N ±0.38, O ±0.39, S ±0.34, Cl ±0.28.

[c] Obtained on a Riber 10–10 spectrometer.

[d] IR (KBr): ν = 1630 cm^{-1} (C=O).

[e] Recorded on a Bruker WP 60 spectrometer.

[f] This signal has been erroneously attributed to H-3.[2] Actually the chemical shift value for H-3 is δ = 7.2, as unambiguously attested by its disappearance in **3h–l**.

mixture for 15 min and stirring is maintained for an additional hour at −20 °C. The reaction mixture is filtered, and the filtrate is evaporated *in vacuo* (at atmospheric pressure for **2e**) to give quantitative yields of the thiocarboxylates **2a–g**.

Alkyl 3-(2-Bromopyridyl) Ketones: The 3-(2-bromopyridyl) methyl ketone **(1a)** is prepared in 47% yield according to the previously described procedure.[2] The 3-(2-bromopyridyl) ethyl and propyl ketones, **(1b)** and **(1c)**, respectively, are synthesized in the same manner by quenching the 2-bromo-3-lithiopyridine with propanal and butanal. The intermediate alcohols are subsequently oxidized with CrO_3 in acetone (Jones reagent) to furnish the desired pyridyl ketones **1b, c** (Table 1), which are obtained as colorless oils after distillation under reduced pressure.

Preparation of 4-Oxo-4*H*-thiopyrano[2,3-*b*]pyridines 3a–l; General Procedure:

To a suspension of NaH (310 mg, 13 mmol) in anhydrous THF (10 mL) are slowly added, with stirring and under argon, the appropriate ketones **1a, b** (12 mmol) dissolved in THF (20 mL). The mixture is maintained at 0 °C for 15 min. A solution of the thiocarboxylates **2a–g** (12 mmol) in anhydrous THF (20 mL) is then added dropwise, and the resultant mixture is stirred under reflux for 2 h. The crude reaction mixture is then poured into cooled (0 °C) H_2O (100 mL). The products are collected by filtration and recrystallized twice from hexane/toluene (70:30) (decolorized with Norit®).

For the experiments performed with the 3-(2-bromopyridyl) ethyl ketone **(1c)**, the reactions are carried out in *N*-methyl-2-pyrrolidone, but the amount of solvent is reduced by half. To induce the cyclocondensation a temperature of 140 °C must be maintained for 2 h. After pouring into cold H_2O (200 mL) the mixture is extracted with EtOAc (3 × 50 mL), and the organic extract is dried with $MgSO_4$. The solvents are removed under reduced pressure. Purification of compounds **3k, l** is achieved by column chromatography on silica gel (Merck, Kieselgel 60, 70–230 mesh) using the mixture EtOAc/hexane (1:1) as eluent.

The authors gratefully acknowledge the financial support of the Centre National de la Recherche Scientifique and Region Nord-Pas de Calais (grant to E.H.).

Received: 14 November 1988

(1) Sliwa, H. *Bull. Soc. Chim. Fr.* **1970**, 642.
(2) Becher, J., Christensen, M.C., Møller, J., Winckelman, I. *Sulfur Lett.* **1982**, *1*, 43.
(3) Reynaud, P., Moreau, R.C., Samana, J.P. *Bull. Soc. Chim. Fr.* **1965**, 3628.
(4) Güngör, T., Marsais, F., Queguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139.
(5) Marsais, F., Laperdrix, B., Güngör, T., Mallet, M., Queguiner, G. *J. Chem. Res. (S)* **1982**, 278; *(M)* 2863.
(6) Couture, A., Grandclaudon, P. *Synthesis* **1985**, 533.