A Facile, One-Pot Synthesis of 2-Arylthiazolo[5,4-*b*]pyridines

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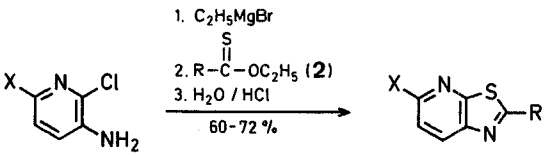
Thiazolopyridines and especially their 2-aryl derivatives are a class of fused heterocycles of considerable interest owing to their analgesic, antipyretic, and anti-inflammatory properties[1]. To our knowledge, such compounds can only be prepared by a few limited methods: either by condensation of aminomercaptopyridines with an aromatic acid chloride[1], or by treatment of hydroxypyridyl-enamides[1] or chloropyridyl-enamides[2] with phosphorus(V) sulfide or Lawesson reagent, respectively. For all these reactions, low yields of conversion have been reported. We therefore directed our investigations towards a novel and effective synthetic approach to these fused heterocyclic systems.

The procedure described here deals with the [5,4-*b*] compounds of this series which are readily accessible by condensation under mild conditions of arenethiocarboxylic *O*-esters **2** with the Grignard reagent of the 2-chloro-3-aminopyridines **1a, b** in tetrahydrofuran. Treatment of the reaction mixture under classical conditions affords the 2-arylthiazolo[5,4-*b*]pyridines **3** with good yields.



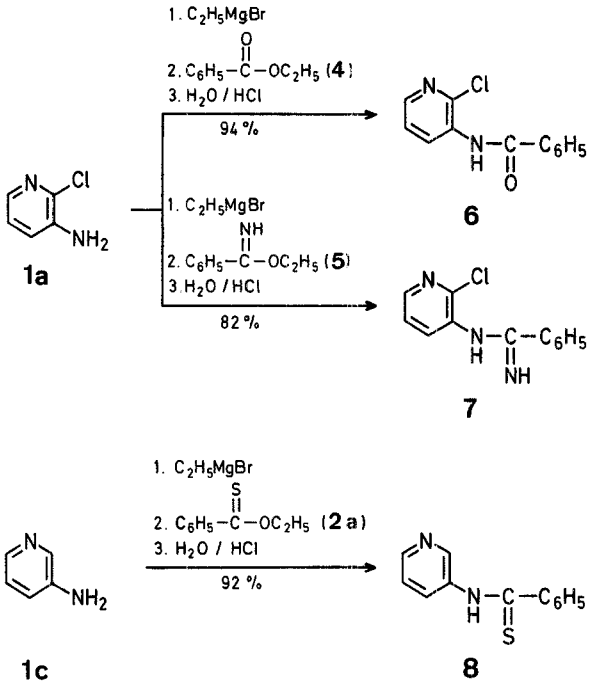
1a X = H
b X = Cl

3a-h

The 3-amino-2-chloropyridines **1a, b** are commercially available. The *O*-ethyl arene- or heteroarenethiocarboxylates **2** can be obtained by the following two methods of equal efficacy:

- reaction of the corresponding ethyl carboxylates with Lawesson reagent in toluene[3];
- conversion of aromatic or heteroaromatic nitriles into the corresponding imidic esters via Pinner reaction[4] and treatment of the ethyl imidates with hydrogen sulfide; this method is well suitable for larger-scale preparations of thioesters **2**, the yields being almost quantitative.

The reaction is specific to thioesters. Thus, the reaction of ethyl benzoate **(4)** or ethyl benzimidate **(5)** with the Grignard reagent of 3-amino-2-chloropyridine under similar conditions affords exclusively 2-chloro-3-benzoylaminopyridine **(6)** and *N*-(2-chloro-3-pyridinyl)-benzamidine **(7)**, respectively. Further, the reaction of *O*-ethyl thiobenzoate **(2a)** with the Grignard reagent obtained from 3-aminopyridine **(1c)** affords *N*-(3-pyridinyl)-thiobenzamide **(8)** in high yield[2]. Thus, the behavior of 3-aminopyridine illustrates the necessity of a Cl substituent on the pyridine ring.



2-Arylthiazolo[5,4-*b*]pyridines 3; General Procedure:

A solution of ethylmagnesium bromide in anhydrous tetrahydrofuran (15 ml) is prepared from ethyl bromide (5.45 g, 50 mmol) and magnesium (1.35 g, 50 mmol). A solution of the 3-amino-2-chloropyridine (**1a, b**; 50 mmol) in tetrahydrofuran (10 ml) is then added dropwise with stirring. To the hot mixture, a solution of the *O*-ethyl thiocarboxylate (**2a–d**; 25 mmol) in anhydrous tetrahydrofuran (5 ml) is added all at once; the resultant mixture is stirred under reflux for 1 h and allowed to stand at room temperature overnight. Then, tetrahydrofuran (50 ml) is added and the mixture poured into dilute hydrochloric acid (100 ml). The organic layer is separated, washed with water (3 × 50 ml), and dried with magnesium sulfate. The solvent is removed under reduced pressure and the residual product recrystallized from toluene/hexane to give the pure product **3**.

3-Benzoylamino-2-chloropyridine (6):

The Grignard reagent of 2-chloro-3-aminopyridine is prepared as described above. A solution of ethyl benzoate (3.75 g, 25 mmol) in tetrahydrofuran (5 ml) is added to the boiling mixture and the reaction is further carried out following the general procedure. The resultant mixture is poured into dilute hydrochloric acid (100 ml). The precipitated amide **6** is isolated by suction, washed with water, and recrystallized from ethanol/water; yield: 5.45 g (94%); m.p. 89–90°C.

$C_{12}H_9ClN_2O$	calc.	C 61.95	H 3.90	N 12.04
(232.6)	found	62.18	3.89	12.00

M.S.: *m/e* = 234, 232 (M^+), 77 (100%).

I.R. (KBr): ν = 3270, 1650 cm^{-1}.

Table. 2-Arylthiazolo[5,4-*b*]pyridines **(3)** prepared from Compounds **1**[a] and **2**[b]

3	R	X	Yield [%]	m.p. [°C][c]	Molecular Formula[d] or m.p. [°C] from Lit.	M.S. (70 eV) *m/e* (M^+) (rel. int.)
a		H	72	121°	$C_{12}H_8N_2S$ (212.3)	212 (100)
b		H	70	170–171°	$C_{12}H_7ClN_2S$ (246.7)	248, 246 (100)
c		H	68	131–132°	$C_{10}H_6N_2OS$ (202.2)	202 (100)
d		H	60	127–128°	$C_{10}H_6N_2S_2$ (218.3)	218 (100)
e		Cl	71	178–179°	177°[5]	248, 247 (100)
f		Cl	67	223–224°	$C_{12}H_6Cl_2N_2S$ (281.2)	282, 280 (89)
g		Cl	66	169–170°	$C_{10}H_5ClN_2OS$ (236.7)	238, 236 (100)
h		Cl	63	179–180°	$C_{10}H_5ClN_2S_2$ (252.7)	254, 252 (100)

[a] Compounds **1** were purchased from Aldrich Chemical Co. and used without further purification.

[b] Compounds **2** were prepared according to Ref.[3,4].

[c] Not corrected.

[d] Satisfactory microanalyses were obtained: C ±0.28; H ±0.22; N ±0.30; S ±0.30; Cl ±0.30.

N-(2-Chloro-3-pyridinyl)-benzamidine (7):

A solution of ethyl benzimidate (3.72 g, 25 mmol) in tetrahydrofuran (10 ml) is allowed to react with the Grignard reagent of **1a** following the general procedure. Dilute hydrochloric acid (100 ml) is then added to the stirred mixture. The aqueous phase is separated, carefully basified with sodium hydrogen carbonate, and extracted with ethyl acetate (2 × 50 ml). The organic extract is washed with water (2 × 50 ml) and dried with sodium sulfate. The solvent is removed under reduced pressure and the remaining crude product **7** recrystallized from heptane/toluene (decolorized with Norit®); yield of pure **7**: 4.75 g (82%); m.p. 71–72°C.

$C_{12}H_{10}ClN_3$	calc.	C 62.21	H 4.35	N 18.14
(231.7)	found	62.00	4.34	17.87

M.S.: *m/e* = 233, 241 (M^+), 104 (100%).

I.R. (KBr): ν = 3300, 3140, 1630 cm^{-1}.

***N*-(3-Pyridinyl)-thiobenzamide (8):**

A solution of ethylmagnesium bromide is prepared from magnesium (0.81 g, 30 mmol) and ethyl bromide (3.27 g, 30 mmol) in tetrahydrofuran (35 ml). A solution of 3-aminopyridine (2.8 g, 30 mmol) in tetrahydrofuran (35 ml) is then added dropwise with stirring. A complex precipitates. Additional tetrahydrofuran (50 ml) is added, followed by the addition in one portion of a solution of *O*-ethyl thiobenzoate (2.49 g, 50 mmol) in tetrahydrofuran (5 ml) to the heated mixture. The resultant mixture is heated at reflux temperature for 1 h, then allowed to stand at room temperature for 8 h. The mixture is cooled and evaporated to dryness under reduced pressure and the remaining crude product stirred with dilute hydrochloric acid (50 ml). The precipitated product **8** is isolated by suction,

washed several times with water, dried at 40 °C under vacuum, and recrystallized from heptane/toluene; yield of pure **8**: 2.95 g (92%); m.p. 140–141 °C.

$C_{12}H_{10}N_2S$	calc.	C 67.27	H 4.70	N 13.07	S 14.96
(214.3)	found	67.53	4.58	12.85	14.91

M.S.: $m/e = 214$ (M^+), 121 (100%).

I.R. (KBr): $\nu = 3120$, 1545 cm^{-1}.

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