Preparation of New Heterocycles from *N*-(1,3-Benzothiazol-2-yl)-2-chloropyridine-3-carboxamides and *N*-(1,3-Thiazol-2-yl)-2-chloropyridine-3-carboxamides

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Only a few reports on the angular [1,3]benzothiazolo[3,2-*a*]quinazoline ring systems are found in the literature[1,2,3]. Analogous systems having the pyrido[2,3-*d*]pyrimidine moiety in place of the quinazoline moiety have hitherto not been described. 5-Oxo-5*H*-[1,3]benzothiazolo[3,2-*a*]quinazolines have recently been prepared from *N*-(1,3-benzothiazol-2-yl)-2-fluorobenzamides[4]. Because of the considerable pharmaceutical interest of compounds containing a combination of the benzothiazole or thiazole and the pyridine ring system, we investigated the synthesis of the title compounds and their cyclization products.

We describe here the synthesis of *N*-(1,3-benzothiazol-2-yl)- **(5)** and *N*-(1,3-thiazol-2-yl)-2-chloropyridine-3-carboxamides **(6)** from 2-chloropyridine-3-carbonyl chloride **(2)** and 2-amino-1,3-benzothiazoles **(3)** or 2-amino-1,3-thiazoles **(4)** respectively, and the cyclization of compounds **5** and **6** to 5-oxo-5*H*-pyrido[3′,2′:5,6]pyrimido[2,1-*b*][1,3]benzothiazoles **(7)** or 5-

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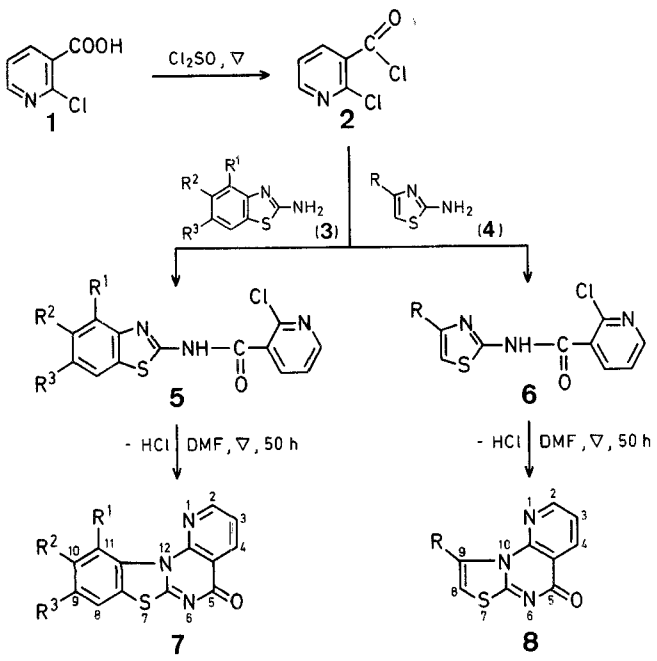

oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidines **(8)**. The cyclization reactions **5** → **7** and **6** → **8** are effected by refluxing compounds **5** or **6**, respectively, in dimethylformamide for 50 h. In the case of compounds **5c** ($R^3 = NO_2$) and **5d** ($R^1 = Cl$), the intramolecular cyclocondensation does not take place even when prolonged reaction times are used, the starting materials being recovered unchanged.

Melting points were determined using a Mettler FP-61 automatic apparatus. Mass spectra were recorded with a Hewlett-Packard 5930-A spectrometer. I.R. spectra were recorded with a Perkin-Elmer 283 instrument. ^{1}H-N.M.R. spectra were obtained with a Perkin-Elmer R-12 spectrometer.

_N_-(1,3-Benzothiazol-2-yl)-2-chloropyridine-3-carboxamides (5) and _N_-(1,3-Thiazol-2-yl)-2-chloropyridine-3-carboxamides (6); General Procedure:

A mixture of 2-chloropyridine-3-carboxylic acid (**1**; 6.3 g, 0.04 mol) and thionyl chloride (24 ml, 0.33 mol) is heated at reflux temperature with vigorous stirring. After 3 h, the acid **1** has completely dissolved. Excess thionyl chloride is distilled off, benzene (20 ml) is added, and the last traces of thionyl chloride are distilled off with the added benzene. The *2-chloropyridine-3-carbonyl chloride* **(2)** thus obtained is dissolved in benzene (100 ml) and this solution added dropwise, with stirring, to a mixture of the 2-amino-1,3-benzothiazole (**3**; 0.04 mol) or 2-

Table 1. *N*-(1,3-Benzothiazol-2-yl)-2-chloropyridine-3-carboxamides **(5)** and *N*-(1,3-Thiazol-2-yl)-2-chloropyridine-3-carboxamides **(6)**

Product	R^1	R^2	R^3	R	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	M.S. (70 eV) *m/e* M^+ (%)	I.R. (Nujol) ν_{NH}	I.R. (Nujol) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS_{int}) δ [ppm]
5a	H	H	H	—	73	259–261° (ethanol)	$C_{13}H_8ClN_3OS$ (289.7)	289 (68)	3190	1675	13.1 (s, 1H, NH); 8.7–7 (m, 7H)
5b	H	H	OCH_3	—	60	251–252° (ethanol)	$C_{14}H_{10}ClN_3O_2S$ (319.7)	319 (10)	3190	1675	8.7–7 (m, 6H); 3.8 (s, 3H, OCH_3)
5c	H	H	NO_2	—	48	249–250.5° (butanol)	$C_{13}H_7ClN_4O_3S$ (334.7)	334 (30)	3190	1675	9–7.4 (m, 6H)
5d	Cl	H	H	—	53	197–199° (ethanol)	$C_{13}H_7Cl_2N_3OS$ (324.2)	324 (12)	3200	1690	8.7–7.1 (m, 6H)
5e	H	CH_3	CH_3	—	76	>300° (butanol)	$C_{15}H_{12}ClN_3OS$ (317.8)	317 (19)	3180	1670	8.7–7.4 (m, 5H); 2.3 (s, 6H, $2CH_3$)
6a	—	—	—	H	84	180° (ethanol)	$C_9H_6ClN_3OS$ (239.7)	239 (39)	3190	1670	8.7 (m, 1H, 6-H); 8.25 (m, 1H, 4-H); 7.65 (d, 1H, 4′-H); 7.6 (m, 1H, 5-H′); 7.4 (d, 1H, 5′-H)
6b	—	—	—	CH_3	75	165° (ethanol)	$C_{10}H_8ClN_3OS$ (253.7)	253 (100)	3180	1670	8.5 (m, 1H, 6-H); 8.05 (m, 1H, 4-H); 7.5 (m, 1H, 5-H); 6.8 (d, 1H, 5′-H); 2.25 (s, 3H, CH_3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.30; H, ±0.25; N, ±0.32.

Table 2. 5-Oxo-5*H*-pyrido[3′,2′:5,6]pyrimido[2,1-*b*][1,3]benzothiazoles **(7)** and 5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidines **(8)**

Product	Yield [%]	m.p. [°C]	Molecular formula[a]	M.S. (70 eV) *m/e* M^+ (%)	I.R. (Nujol) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (TFA-*d*/TMS_{int}) δ [ppm]
7a	60	244–245°	$C_{13}H_7N_3OS$ (253.3)	253 (100)	1650	9.9 (m, 1H, 11-H); 9.3 (m, 1H, 2-H); 9.0 (m, 1H, 4-H); 8.3–7.8 (m, 4H)
7b	62	249–250°	$C_{14}H_9N_3O_2S$ (283.3)	283 (100)	1640	9.8 (m, 1H, 11-H); 9.3 (m, 1H, 2-H); 9.0 (m, 1H, 4-H); 8.2–7.5 (m, 3H); 4.1 (s, 3H, OCH_3)
7e	79	293–295°	$C_{15}H_{11}N_3OS$ (281.3)	281 (100)	1650	9.8 (s, 1H, 11-H); 9.4 (m, 1H, 2-H); 9.1 (m, 1H, 4-H); 8.3–7.7 (m, 2H); 2.7 (s, 3H, CH_3); 2.6 (s, 3H, CH_3)
8a	71	283–285°	$C_9H_5N_3OS$ (203.2)	203 (100)	1640	9.25 (m, 1H, 2-H); 9.1 (d, 1H, 9-H); 9.05 (m, 1H, 4-H); 8.1 (m, 1H, 3-H); 7.9 (d, 1H, 8-H)
8b	60	296–297°	$C_{10}H_7N_3OS$ (217.2)	217 (100)	1635	9.2 (m, 1H, 2-H); 9.05 (m, 1H, 4-H); 8.05 (m, 1H, 3-H); 7.45 (s, 1H, 8-H); 3.3 (s, 3H, CH_3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.23; H, ±0.22; N, ±0.27.

amino-1,3-thiazole (**4**; 0.04 mol) and triethylamine (4.04 g, 0.04 mol) in benzene (100 ml). After the addition is complete the mixture is heated at reflux temperature for 3 h, and then cooled. The solid product **5** or **6** is isolated by suction, dried, and purified by recrystallization.

5-Oxo-5*H*-pyrido[3′,2′:5,6]pyrimido[2,1-*b*][1,3]benzothiazoles (7) and 5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidines (8); General Procedure:

The *N*-substituted 2-chloropyridine-3-carboxamide **5** or **6** (2 mmol) is dissolved in dimethylformamide (10 ml) and this solution heated at reflux temperature for 50 h. On cooling of the mixture, products **7** or **8** precipitate as fine needles. The precipitate is isolated by suction and washed with ethanol.

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