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Pyridazines, LIV [1]: On the Synthesis of Pyridazine-Fused S-Heterocycles: Thieno[2,3-c]pyridazine, Pyrimido[4′,5′ : 4,5]thieno[2,3-c]pyridazine, and Pyridazino[3,4-b][1,4]benzothiazine

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Summary. Starting from 3-chloro-4-pyridazinecarbonitrile (**1**), the thienopyridazine derivatives **2** and **3** were prepared. Condensation of **3** with triethyl orthoformate afforded the novel tricyclic system **4**. Reaction of **1** with 2-aminothiophenol, followed by treatment with NaH/*DMSO* was found to give the diaza-phenothiazine **6** instead of the expected condensed thiazepine.

Keywords. 3-Chloro-4-pyridazinecarbonitrile, reactions with S-nucleophiles; Pyridazino[3,4-b]-[1,4]benzothiazine; Pyrimido[4′,5′ : 4,5]thieno[2,3-c]pyridazine; Thieno[2,3-c]pyridazine derivatives.

Pyridazine, 54. Mitt.: Zur Synthese pyridazin-anellierter S-Heterocyclen: Thieno[2,3-c]pyridazin, Pyrimido[4′,5′ : 4,5]thieno[2,3-c]pyridazin und Pyridazino[3,4-b][1,4]benzothiazin

Zusammenfassung. Aus 3-Chlor-4-pyridazincarbonitril (**1**) wurden die Thienopyridazin-Derivate **2** und **3** dargestellt. Das neue tricyclische System **4** wurde durch Kondensation von **3** mit Triethylorthoformiat erhalten. Reaktion von **1** mit 2-Aminothiophenol, gefolgt von Umsetzung mit NaH/*DMSO* lieferte anstelle des erwarteten Thiazepin-Derivates das Diaza-Phenothiazin **6**.

Introduction

Whereas pyridine-annelated sulfur-containing heterocycles have been studied extensively [3], comparatively little is known about aza-analogous systems in which an S-heterocycle is fused to a pyridazine nucleus. In continuation of our previous efforts towards the preparation of condensed pyridazines as aza-isosters of pharmaceutically relevant bi- and tricycles, we here report on efficient syntheses of some representatives of the title ring systems, employing 3-chloro-4-pyridazinecarbonitrile [4, 5] (**1**) as the starting material. The versatility of this conveniently accessible bifunctional educt for the construction of various heterocycle-fused pyridazines

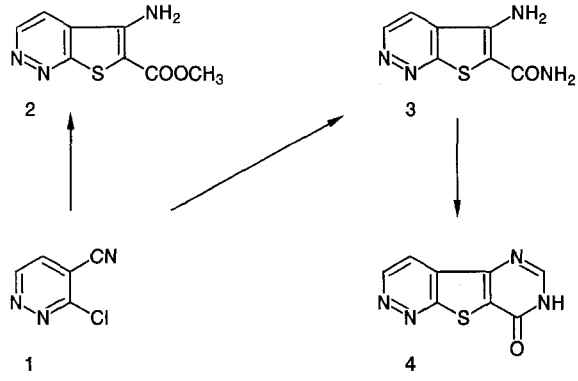
* Dedicated with best wishes to Prof. Dr. G. Zigeuner on the occasion of his 70th anniversary

lacking additional substituents in the 1,2-diazine moiety has been demonstrated recently [6].

Results and Discussion

Reaction of the chloro nitrile **1** with methyl mercaptoacetate in the presence of a base (potassium carbonate) was found to proceed smoothly to give the pyridazine-fused thiophene derivative **2** in high yield [11].

In view of reported syntheses of benzothieno[3,2-d]pyrimidines [18] and aza-analogues thereof (pyrido[3′,2′ : 4,5]thieno[3,2-d]pyrimidines [12], pyrazino-[2′,3′ : 4,5]thieno[3,2-d]pyrimidines [15], pyrimido[4′,5′ : 4,5]thieno[2,3-b]-quinolines [16]), the amino ester **2** was considered a useful educt for the construction of the hitherto unknown pyrimido[4′,5′ : 4,5]thieno[2,3-c]pyridazine ring system. Unexpectedly, attempted pyrimidine ring closure by refluxing **2** in formamide solution gave mainly decomposition products. Moreover, we initially failed in the preparation of the corresponding amide **3** which was anticipated a more appropriate cyclization precursor: heating of the ester **2** in ethanolic ammonia gave only traces of **3**. However, the amide **3** was found to be conveniently accessible (yield > 80%) by employing mercaptoacetamide in the annelation of the thiophene ring to the pyridazine nucleus. Similar to previous observations in the thieno[2,3-b]- and thieno[2,3-c]pyridine series [14], refluxing of the amino amide **3** in triethyl orthoformate finally afforded the novel tricyclic system **4**.



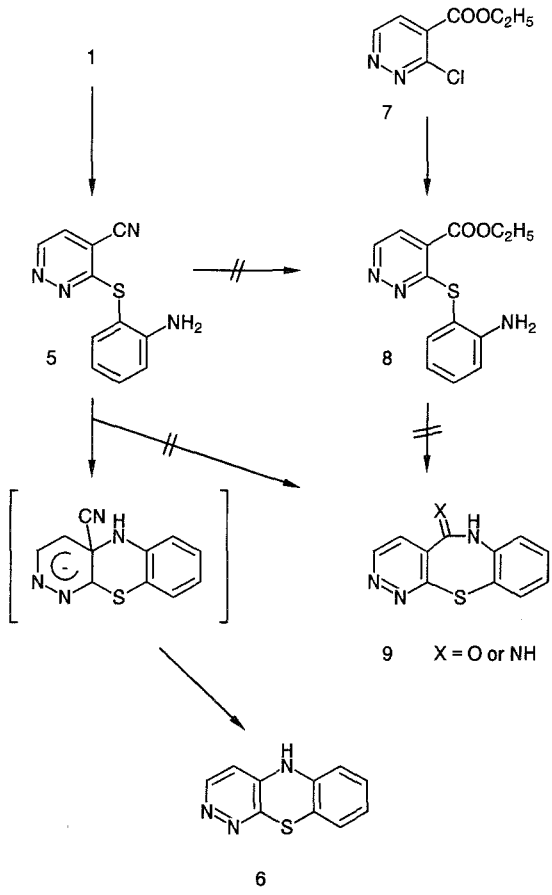
Like in the reactions of **1** with mercaptoacetic acid derivatives, smooth nucleophilic substitution of the chloro function in **1** as well as in the corresponding ester **7** (available according to Ref. [4]) was observed on treatment with 2-aminothiophenol as a bifunctional nucleophile. The products **5** and **8** thus obtained [19] appeared to be of interest with respect to the preparation of pyridazino-[3,4-b][1,5]benzothiazepines, representing a tricyclic ring system of potential pharmaceutical utility.

In contrast to known cyclization reactions of related thiophene derivatives [20, 21], the ester **8** so far could not be transformed into the tricyclic system **9** nor did the nitrile **5** provide an access to this type of compounds. Under various reaction conditions, the nitrile **5** yielded only undefined mixtures; similar unsatisfactory

results were obtained upon treatment of the ester **8** with sodium methylsulfinylmethanide (prepared in situ according to Ref. [22]). Under the latter conditions, the nitrile **5**, however, afforded an 85% yield of a well-defined reaction product.

Surprisingly, the elemental composition $C_{10}H_7N_3S$ together with the mass spectrum (M^+ at $m/z=201$) indicated the elimination of a HCN fragment from **5**. Thus, the pyridazino[3,4-b][1,4]benzothiazine structure **6** has to be assigned to the new compound. Obviously, the amino function (or the corresponding anion, respectively) in **5** does not attack the nitrile function but adds to C-4 of the π-deficient heteroarene. Rearomatization of the intramolecular σ-adduct thus formed then is gained by C−CN bond fragmentation.

Whereas several pyridazino[3,4-b][1,4]benzothiazines bearing various substituents at C-3 and N-5 have been reported in the literature [23], to our knowledge the parent system has not been described to date [24]. Considering the 67% yield of compound **5** from **1**, the reaction **5** → **6** discovered in the present study gives rise to an efficient access to the novel diaza-phenothiazine **6**.



Experimental Part

Melting points (uncorrected) were determined on a Kofler hot-stage microscope. ^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz) or a Bruker AC 80 (80 MHz) spectrometer (*TMS* as

internal reference, δ-values in ppm), mass spectra on a Finnigan MAT 311 A and on a Finnigan MAT 8230 (with data system SS 300), IR spectra on a Jasco IRA-1 (KBr disks; cm^{-1}). Column chromatography was carried out on Merck Kieselgel 60, 0.063 – 0.200 mm (70 – 230 mesh ASTM). Light petroleum refers to the fraction of b. p. 50 – 70°C. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

Methyl 5-Aminothieno[2,3-c]pyridazine-6-carboxylate (**2**)

A mixture of 279 mg (2 mmol) **1** [4, 5], 424 mg (4 mmol) methyl mercaptoacetate, and 434 mg (3 mmol) potassium carbonate in 30 ml dimethylformamide was stirred at room temperature for 24 h. After filtration, the solvent was removed *in vacuo* and the residue was extracted several times with boiling ethyl acetate. Evaporation of the combined extracts, followed by digeration with little methanol afforded 350 mg (84%) of yellow crystals; m. p. = 228 – 230°C (decomp.; from methanol). $C_8H_7N_3O_2S$ (209.22); calcd. C 45.93, H 3.37, N 20.08; found C 45.92, H 3.47, N 20.07. IR: 1 690 (C=O). ^{1}H-NMR (*DMSO-d*$_6$): δ = 9.40 (d, *J* = 6.0 Hz, 1 H, H-3), 8.45 (d, *J* = 6.0 Hz, 1 H, H-4), 7.50 (broad s, 2 H, NH_2), 3.87 (s, 3 H, CH_3).

3-Aminothieno[2,3-c]pyridazine-6-carboxamide (**3**)

A mixture of 279 mg (2 mmol) **1** [4, 5], 364 mg (4 mmol) mercaptoacetamide, and 434 mg (3 mmol) potassium carbonate in 30 ml dimethylformamide was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was digerated in water, filtered, and dried to give 320 mg (82%) of yellow crystals; m. p. = 310 – 320°C (decomp.; from 1-propanol). $C_7H_6N_4OS$ (194.21); calcd. C 43.29, H 3.11, N 28.85; found C 43.38, H 3.20, N 28.54. IR: 1 660 (C=O). ^{1}H-NMR (*DMSO-d*$_6$): δ = 9.33 (d, *J* = 6.0 Hz, 1 H, H-3), 8.32 (d, *J* = 6.0 Hz, 1 H, H-4), 7.45, 7.30 (broad s, 1 H each, NH_2).

Pyrimido[4',5' : 4,5]thieno[2,3-c]pyridazin-8(7H)-one (**4**)

A suspension of 194 mg (1 mmol) **3** in 5 ml triethyl orthoformate was refluxed for 24 h. The mixture was evaporated *in vacuo* and the residue was recrystallized from dimethylformamide/water to afford 174 mg (85%) of colourless crystals; m. p. > 330°C (decomp.). $C_8H_4N_4OS$ (204.21); calcd. C 47.05, H 1.97, N 27.44; found C 46.97, H 2.08, N 27.44. IR: 1 650 (C=O). ^{1}H-NMR (*DMSO-d*$_6$): δ = 14.0 – 12.0 (broad, 1 H, NH), 9.51 (d, *J* = 5.8 Hz, 1 H, H-3), 8.47 (d, *J* = 5.8 Hz, 1 H, H-4), 8.46 (s, 1 H, H-7).

3-(2-Aminophenylthio)-4-pyridazinecarbonitrile (**5**)

A mixture of 558 mg (4 mmol) **1**, 1.00 g (8 mmol) 2-aminothiophenol, and 672 mg (8 mmol) sodium hydrogencarbonate in 20 ml abs. ethanol was stirred for 2 h at room temperature under an atmosphere of argon. The yellow precipitate was collected, washed with ethanol and water, dried, and recrystallized from toluene to afford 612 mg (67%) of yellow crystals; m. p. = 150 – 152°C. $C_{11}H_8N_4S$ (228.27); calcd. C 57.88, H 3.53, N 24.54; found C 58.00, H 3.67, N 24.41. IR: 2 240 (C≡N). ^{1}H-NMR (*DMSO-d*$_6$): δ = 9.23 (d, *J* = 6.0 Hz, 1 H, H-6), 8.12 (d, *J* = 6.0 Hz, 1 H, H-5), 7.4 – 6.5 (m, 4 H, C_6H_4), 5.50 (broad s, 2 H, NH_2).

5H-Pyridazino[3,4-b][1,4]benzothiazine (**6**)

A solution of 300 mg (10 mmol) sodium hydride (80% suspension in paraffin) in 15 ml *DMSO* was heated to 70°C for 10 min. After the initial effervescence had ceased, the mixture was cooled to 0°C and a suspension of 456 mg (2 mmol) **5** in 20 ml *DMSO* was added dropwise. The reaction mixture

was stirred at room temperature for 15 min, then it was poured onto ice-water and extracted exhaustively with dichloromethane. The residue left on evaporation of the extract was purified by column chromatography (dichloromethane/methanol, 19 + 1). Subsequent recrystallisation from ethyl acetate yielded 342 mg (85%) of pale yellow crystals; m. p. = 242 – 244°C. $C_{10}H_7N_3S$ (201.25); calcd. C 59.68, H 3.51, N 20.89; found C 59.39, H 3.58, N 20.67. ^{1}H-NMR (*DMSO-d_6*): δ = 9.32 (broad s, 1 H, NH), 8.38 (d, *J* = 5.6 Hz, 1 H, H-4), 7.1 – 6.6 (m, 4 H, H-6, H-7, H-8, H-9), 6.43 (d, *J* = 5.6 Hz, 1 H, H-3). Ms: *m/z* = 201 (M^+, 100%).

Ethyl 3-(2-Aminophenylthio)-4-pyridazinecarboxylate (**8**)

A mixture of 373 mg (2 mmol) ethyl 3-chloro-4-pyridazinecarboxylate [4] **7**, 500 mg (4 mmol) 2-aminothiophenol, and 336 mg (4 mmol) sodium hydrogencarbonate in 15 ml abs. ethanol was stirred for 4 h at room temperature under an atmosphere of argon. After filtration, the solvent was removed *in vacuo*. Column chromatography (ethyl acetate/light petroleum, 1 + 1), followed by recrystallisation from ethyl acetate/light petroleum afforded 170 mg (31%) of yellow crystals; m. p. = 103 – 106°C. $C_{13}H_{13}N_3O_2S$ Hr-ms: calcd. 275.0737; found 275.0730. IR: 1 715 (C = O). ^{1}H-NMR ($CDCl_3$): δ = 9.01 (d, *J* = 5.0 Hz, 1 H, H-6), 7.76 (d, *J* = 5.0 Hz, 1 H, H-5), 7.5 – 6.5 (m, 4 H, C_6H_4), 4.45 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.30 (broad s, 2 H, NH_2), 1.42 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

Acknowledgement

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