5,6,7,8-Tetrahydropyrido[4,3-*c*]pyridazine: A Lead-Oriented Scaffold with Two Diversity Points

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Abstract: An approach to the derivatives of 5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazine, a lead-oriented scaffold with two diversity points, was developed. The method included five steps starting from the readily available 4-piperidone derivatives and allowed for the preparation of the target compounds in 32–35% overall yields. The key step of the sequence included one-pot solvent-free reaction of the corresponding 4-piperidone derivative, glyoxylic acid, and hydrazine.

Key words: nitrogen heterocycles, pyridazine, piperidine, nucleophilic substitution, lead-oriented synthesis

Pyridazine derivatives have attracted much interest in the search for new drugs.[1] In a recent review by Wermuth, they were recognized as privileged structures for drug discovery.[2] Recently, pyridazine-based scaffolds were proposed as possible analogues of nucleobases[3] and α-helix mimetics.[4]

Recent tendencies in drug discovery are shifting towards using sp^3-enriched conformationally restricted low-molecular-weight templates as starting points in the design of potential lead compounds.[5] Fusion of the pyridazine ring with a saturated heterocycle (e.g., piperidine) can generate scaffolds of enhanced interest to drug discovery. In this work, we propose an example of such a scaffold, namely, 5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazine (**1**) (Figure 1). It is important to note that apart from the secondary amine function of the piperidine ring, which can be easily modified using the methods of combinatorial chemistry, **1** contains an additional hidden diversity point related to the pyridazine fragment. In particular, libraries of compounds of general formula **2** or **3** can be designed. Moreover, the values of relevant physicochemical properties of **1** (MW 135.2; Fsp^3 0.43; cLogP –0.60; TPSA 37.81 Å^2)[6] are well below the common limits for the molecular fragments, such as 'rule of three'.[7] Therefore, **1** represents an example of a bifunctional conformationally restricted scaffold[8] potentially useful for lead-oriented synthesis.[9]

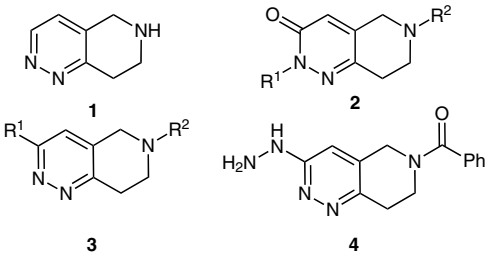
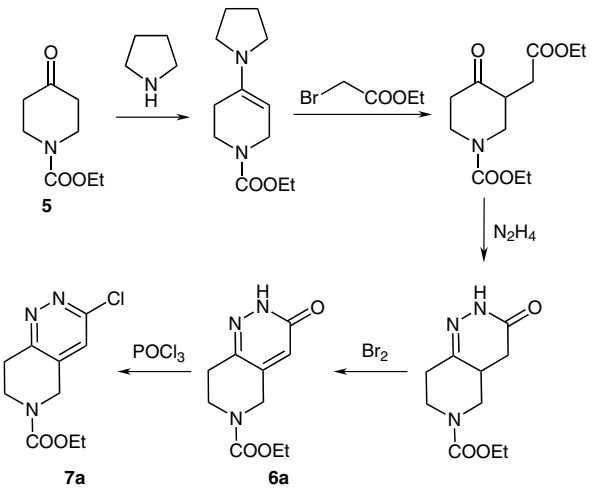


Figure 1

Derivatives of **1** have already proven their efficiency in drug discovery: in the 1970s, endralazine (**4**) was introduced as an antihypertensive agent.[10] Surprisingly, almost no attention has since been paid to the synthesis of derivatives of general formula **2** or **3**. The known approach commenced from the 4-piperidone derivative **5**;[11] it was transformed into compound **6** in four steps (Scheme 1). Further modifications of **6** were limited to the synthesis of endralazine (**4**) or its analogues, which were prepared via reaction of the chloride **7** with hydrazine.



Scheme 1 Synthesis of 5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazines reported in the literature

Instead of using the four-step sequence reported in the literature,[10,11] we have developed a simple one-pot procedure for the preparation of the pyridazinone **6**. The

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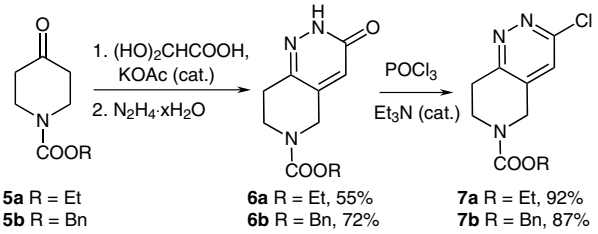
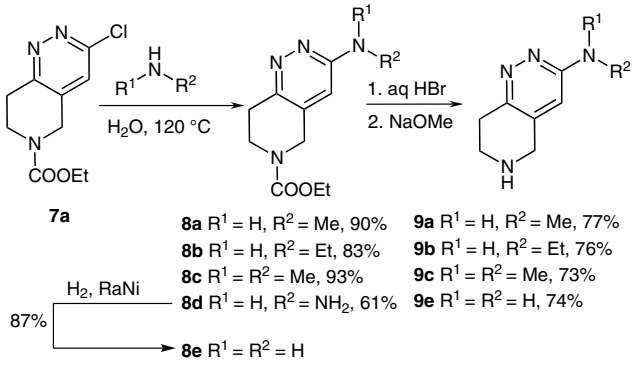
method commenced from **5a** or **5b**, which can be easily obtained by derivatization of commercially available 4-piperidone hydrochloride with the corresponding chloroformate.[12] The key step in the synthesis included heating of **5** with glyoxylic acid monohydrate in the presence of a catalytic amount of potassium acetate without solvent at 80 °C, followed by careful addition of hydrazine hydrate (Scheme 2).[13] Although the yield of **6a** and **6b** was moderate (55–72%), the robustness of the synthetic operations as well as the availability of the starting materials made this method preferable.



Scheme 2 Synthesis of intermediates **6** and **7**

Reaction of **6a** or **6b** with phosphoryl chloride in the presence of a catalytic amount of triethylamine gave chlorides **7a** and **7b** in 92% and 87% yields, respectively. The reactivity of **7** towards nucleophilic substitution of the chlorine atom was low. In particular, reaction of **7a** with N-nucleophiles (such as aliphatic amines and hydrazine) was accomplished only by heating in an autoclave at 120 °C or by microwave irradiation (Scheme 3). Nevertheless, the corresponding derivatives **8a–d** were obtained in 60–95% yields. Reaction of **7** and liquid ammonia or its aqueous solution did not give satisfactory results under any conditions studied; nevertheless, compound **8e** was easily obtained from **8d** in 78% yield using catalytic hydrogenation. Deprotection of **8** by acidic hydrolysis gave the corresponding amines **9a–e** (73–77% yields).



Scheme 3

In conclusion, a convenient five-step reaction sequence was developed for the synthesis of 3-substituted 5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazine derivatives, starting from readily available 4-piperidones, in 32–35% overall yields.

The solvents were purified according to standard procedures. All starting materials were purchased from Acros, Merck, Fluka, or UORSY. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer [500 MHz (^{1}H) and 125 MHz (^{13}C)], downfield from TMS (^{1}H, ^{13}C) as an internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument [chemical ionization (APCI) and Agilent 5890 Series II 5972 GCMS instrument [electron impact ionization (EI)].

Alkyl 3-Oxo-3,5,7,8-tetrahydropyrido[4,3-*c*]pyridazine-6(2*H*)-carboxylates 6a,b; General Procedure

Glyoxalic acid monohydrate (47 g), KOAc (2 g), and piperidone **5** (0.5 mol) were added to a 1-L reactor equipped with a mechanical stirrer. The resulting mixture was heated at 80 °C (internal temperature control) for 3 h. Hydrazine hydrate (27.5 mL) was added portionwise with stirring (CAUTION! Very exothermic reaction). After the vigorous reaction had ceased, the mixture was stirred for an additional 10 min, diluted with MeOH (400 mL), and cooled to r.t. The precipitate was filtered off and washed with MeOH (40 mL) to give pure **6**.

Ethyl 3-Oxo-3,5,7,8-tetrahydropyrido[4,3-*c*]pyridazine-6(2*H*)-carboxylate (6a)

White powder; yield: 207 g (55%); mp 174–176 °C (Lit.[11] 165–168 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.81 (br s, 1 H), 6.78 (s, 1 H), 4.50 (s, 2 H), 4.09 (q, J = 7.0 Hz, 2 H), 3.64 (t, J = 6.0 Hz, 2 H), 2.72 (t, J = 6.0 Hz, 2 H), 1.21 (t, J = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.4, 154.6, 142.4, 140.2, 124.9, 61.1, 43.8, 40.9, 28.0, 14.6.

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.97; H, 5.60; N, 18.74.

Benzyl 3-Oxo-3,5,7,8-tetrahydropyrido[4,3-*c*]pyridazine-6(2*H*)-carboxylate (6b)

White powder; yield: 42 g (72%); mp 187–189 °C .

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.33 (s, 1 H), 7.06–6.72 (m, J = 14.0 Hz, 5 H), 6.28 (s, 1 H), 4.61 (s, 2 H), 4.02 (s, 2 H), 3.15 (s, 2 H), 2.22 (s, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.39, 154.45, 142.36, 136.65, 128.39, 127.87, 127.60, 124.92, 66.52, 43.86, 27.97.

MS (CI): m/z = 286 (M + H$^+$).

Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.20; H, 5.34; N, 14.74.

Alkyl 3-Chloro-7,8-dihydropyrido[4,3-*c*]pyridazine-6(5*H*)-carboxylates 7a,b; General Procedure

$POCl_3$ (150 mL) and Et_3N (0.5 mL) were added to **6** (0.2 mol). The resulting mixture was heated under an argon atmosphere at 80 °C for 3 h, and then cooled. Most of the $POCl_3$ was removed in vacuo, and the residue was poured into a mixture of ice (1 kg) and 25% aq NH_3 (1 L). The product was extracted with $CHCl_3$ (500 mL). The extract was dried (Na_2SO_4) and evaporated in vacuo. The brownish residue contained >98% of the target compound. After purification of the crude product by flash chromatography ($CHCl_3$), pure **7** was obtained. Alternatively, **7** can be purified by recrystallization (MeOH).

Ethyl 3-Chloro-7,8-dihydropyrido[4,3-*c*]pyridazine-6(5*H*)-carboxylate (7a)

White solid; yield: 48 g (92%); mp 109–111 °C (MeOH) (Lit.[11] 105–107 °C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.83 (s, 1 H), 4.66 (s, 2 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.74 (t, J = 6.0 Hz, 2 H), 3.09 (t, J = 6.0 Hz, 2 H), 1.23 (t, J = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.4, 154.6, 153.7, 137.1, 125.3, 61.2, 43.5, 40.2, 28.8, 14.5.

MS (CI): *m*/*z* = 242/244 (M + H$^+$).

Anal. Calcd for $C_{10}H_{12}ClN_3O_2$: C, 49.70; H, 5.00; Cl, 14.67; N, 17.39. Found: C, 49.91; H, 4.69; Cl, 14.73; N, 17.05.

Benzyl 3-Chloro-7,8-dihydropyrido[4,3-*c*]pyridazine-6(5*H*)-carboxylate (7b)
White solid; yield: 27 g (87%); mp 95–97 °C (MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.85 (s, 1 H), 7.39 (s, 5 H), 5.15 (s, 2 H), 4.72 (s, 2 H), 3.79 (s, 2 H), 3.11 (s, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.88, 154.94, 154.23, 137.55, 137.08, 134.68, 128.91, 128.42, 128.16, 125.93, 79.66, 67.16, 44.08, 40.92, 29.31.

MS (CI): *m*/*z* = 304/306 (M + H$^+$).

Anal. Calcd for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; Cl, 11.67; N, 13.83. Found: C, 49.91; H, 4.69; Cl, 14.73; N, 17.05.

Ethyl 3-Amino-7,8-dihydropyrido[4,3-*c*]pyridazine-6(5*H*)-carboxylates 8a–d; General Procedure Method A
Compound **7a** 1.21 g (5 mmol), the corresponding amine (15 mmol, concd in H_2O), and LiCl (30 mg) were sealed in a 5-mL MW vial and irradiated in a Emrys Creator™ microwave oven at 120 °C and normal absorption level for 10 min. Then the vial was unsealed, and the mixture was diluted with 5% aq $NaHCO_3$ (10 mL). The precipitate formed was filtered, washed with H_2O (1 mL), and dried. The crude product **8** was of >95% purity. Analytical samples were obtained by flash chromatography (gradient $CHCl_3$–EtOAc). Characterization of **8b**–**d** is given in the supplementary information.

Ethyl 3-Amino-7,8-dihydropyrido[4,3-*c*]pyridazine-6(5*H*)-carboxylates 8a–d; General Procedure Method B
Chloride **7a** (121 g, 0.5 mol), the corresponding amine (1.5 mol, concd in H_2O), and LiCl (1 g) were sealed in an autoclave and heated with stirring at 120 °C for 5 h. The mixture was cooled, diluted with a soln of K_2CO_3 (35 g) in H_2O (200 mL), and the product was extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried (K_2CO_3) and evaporated in vacuo. The residue was purified by flash chromatography (gradient $CHCl_3$–EtOAc) to give **8**. Characterization of **8b**–**d** is given in the Supporting Information.

Ethyl 3-(Methylamino)-7,8-dihydropyrido[4,3-*c*]pyridazine-6(5*H*)-carboxylate (8a)
Brownish crystals; Method A: yield: 1.09 g (93%); Method B: yield 106 g (90%); mp 175–177 °C .

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.59 (s, 1 H), 6.45 (br s, 1 H), 4.49 (s, 2 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 3.67 (t, *J* = 5.6 Hz, 2 H), 2.89 (t, *J* = 5.6 Hz, 2 H), 2.84 (d, *J* = 3.9 Hz, 3 H), 1.23 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.7, 154.7, 147.4, 133.5, 109.9, 61.0, 43.8, 41.3, 28.5, 28.0, 14.5.

MS (CI): *m*/*z* = 237 (M + H$^+$).

Anal. Calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 56.17; H, 7.04; N, 23.88.

Ethyl 3-Amino-7,8-dihydropyrido[4,3-*c*]pyridazine-6(5*H*)-carboxylate (8e)
Raney Ni (15 g) was added to a soln of **8d** (50 g) in EtOH (300 mL). The mixture was degassed and then hydrogenated at 1 bar and 45 °C for 48 h. The catalyst was filtered off over a glass fiber pad and washed thoroughly with EtOH. The combined filtrates were evaporated in vacuo, and the residue was purified by flash chromatography (EtOAc–$CHCl_3$, 1:1) to give **8e** as yellowish crystals; yield: 87%; mp 144–145 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.56 (s, 1 H), 6.15 (s, 2 H), 4.45 (s, 2 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 3.66 (t, *J* = 5.6 Hz, 2 H), 2.86 (t, *J* = 5.6 Hz, 2 H), 1.20 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.0, 155.2, 148.0, 134.2, 110.4, 61.5, 44.4, 41.7, 29.0, 15.1.

MS (CI): *m*/*z* = 223 (M + H$^+$).

Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.30; H, 6.06; N, 25.39.

5,6,7,8-Tetrahydropyrido[4,3-*c*]pyridazin-3-amines 9; General Procedure
Pyridazine **8** (0.5 mol) was dissolved in 47% aq HBr (230 mL, 2 mol). The resulting mixture was refluxed under argon atmosphere for 12 h, then cooled and evaporated in vacuo. The residue was triturated with *i*-PrOH (300 mL), the solid was filtered, washed with *i*-PrOH (100 mL) and dried in vacuo to give **9**·2 HBr as the hydrobromide. Unlike the corresponding hydrochlorides, **9**·2 HBr were not hygroscopic. Characterization of **9b**–**d**·2 HBr is given in the Supporting Information.

To obtain **9** as a free base, **9**·2 HBr (0.1 mol) was treated with 1 M NaOMe in MeOH (0.2 mol). The precipitate was filtered, and the filtrate was evaporated in vacuo. The solid residue was extracted with $CHCl_3$ (3 × 100 mL), and the combined extracts were evaporated in vacuo to give **9**. Characterization of **9b**–**d** is given in the Supporting Information.

***N*-Methyl-5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazin-3-amine (9a)**
Yellowish crystals; yield: 67 g (77%); mp 150–152 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.48 (s, 1 H), 6.44 (s, 1 H), 3.72 (s, 2 H), 2.97 (d, *J* = 4.7 Hz, 2 H), 2.81 (d, *J* = 4.7 Hz, 3 H), 2.75 (d, *J* = 5.5 Hz, 2 H), 2.43 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.9, 146.7, 137.6, 119.3, 95.9, 43.2, 29.3, 25.2.

MS (CI): *m*/*z* = 165 (M + H$^+$).

Anal. Calcd for $C_8H_{12}N_4$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.25; H, 7.19; N, 34.43.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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