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AN UNUSUAL CASCADE REACTION YIELDING *ORTHO-PERI*-FUSED THIENOPYRIDOPYRIMIDINES

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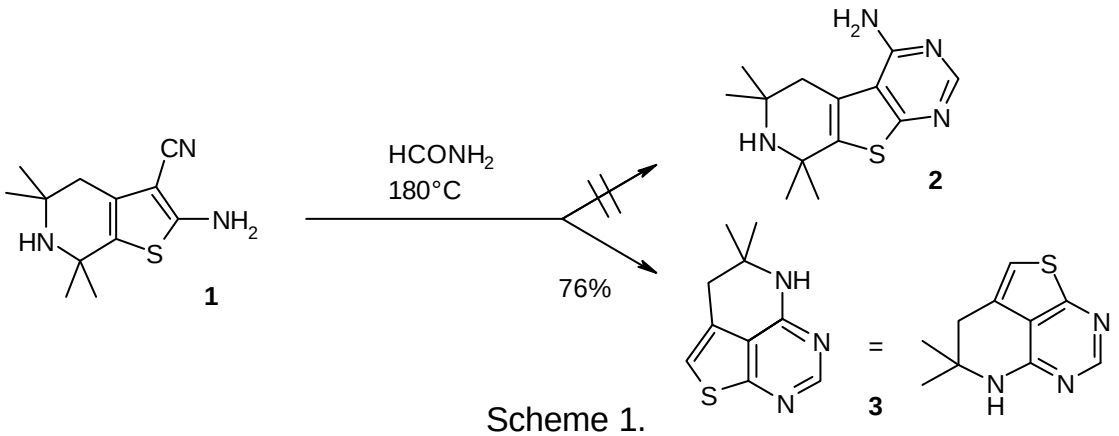
Abstract - A cascade-like ring transformation of a thieno[2,3-*d*]pyridine derivative is reported and mechanistically explained. The product is a novel heterocyclic system consisting of a thiophene ring *peri*-fused with a pyrido[2,3-*d*]pyrimidine moiety. Various derivatives of the new ring system were prepared.

INTRODUCTION

Recently we dealt with thieno-fused tetramethylpiperidine derivatives such as the easily available amino nitrile (**1**) that was derivatized under retention of the sterically slightly strained tetrahydropyridine ring.[1] Since the condensation of *ortho*-amino nitriles with boiling formamide is a well-known method of preparing 4-aminopyrimidines,[2] heating the amino nitrile (**1**) in formamide should give the linear condensation product (**2**). Instead, however, the novel *ortho-peri*-fused thienopyridopyrimidine (**3**) was formed in high yield under these conditions (Scheme 1).

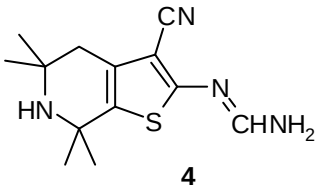


Scheme 1.

The following investigations were done in order to understand this unusual reaction and, based on this knowledge, to develop a general method for preparing other derivatives of the new ring system.

MECHANISTIC ASPECTS

Remarkably, three carbon atoms are being "lost" in the course of the reaction. In fact, ammonia and acetone or its imine were caught in a cold trap and turned out to be main products of the reaction as well. Only traces of the originally expected linear thienopyrimidine (**2**)[1] are formed under these conditions. Though the transformation from the aminothiophene (**1**) to the tricycle (**3**) was performed as a one-pot procedure, it is obviously a multistep reaction with a complex mechanism. Concerning the formation of the pyrimidine ring, two alternative intermediates seemed to be likely: the formamidine (**4**) or the corresponding formamide (**5a**). Since heating the formamidine (**4**)[1] in formamide did not afford any transformation product (**3**) but only the "normal" pyrimidine (**2**), any involvement of the formamidine (**4**) in the formation of **3** is excluded. On the other hand, the corresponding acetamide (**5b**),[1] upon heating with formamide, gave mainly the *ortho-peri*-fused 7-methyl derivative (**6**), along with a minor amount of **3**. Consequently, the formation of the novel tricycles (**3**) and (**6**) proceeds *via* the intermediate amides (**5a**) and (**5b**), respectively.



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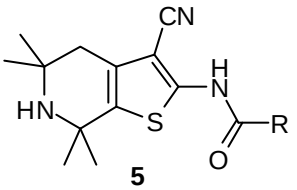

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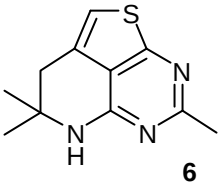

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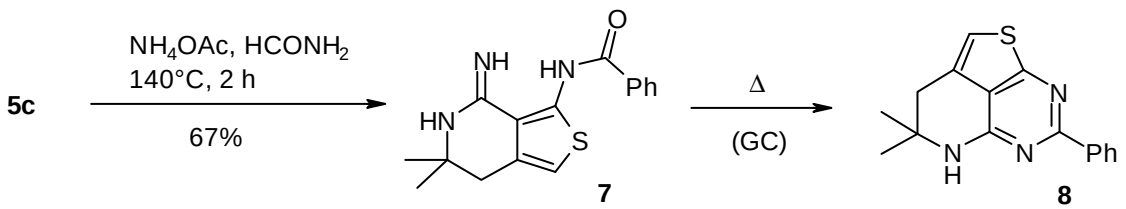
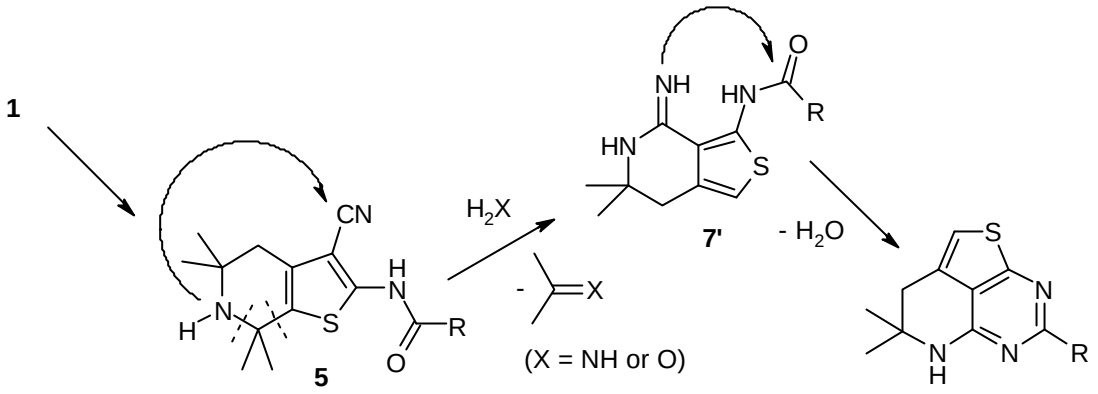
5a: R = H; **5b**: R = Me; **5c**: R = Ph

Further experiments showed that the ring transformation of the thienylformamide (**5a**) to the tricycle (**3**) is proton-catalyzed. In addition, the reaction proceeded readily with *N*-methylformamide as solvent in the presence of acetic acid. This experiment using an ammonia-free reaction medium (in contrast to the use of formamide) indicates clearly that all three nitrogen atoms of compound (**3**) come from the starting material (**1**). During an attempt to synthesize the 7-phenyl derivative (**8**) from the corresponding benzamide (**5c**), the amidine (**7**) crystallized from the reaction mixture. This amidine (**7**) gave GC-IR and GC-MS signals completely identical with those of the thienopyridopyrimidine (**8**) prepared as described below. Consequently, compound (**8**) is formed by cyclization of the intermediate amidine (**7**) (Scheme 2).



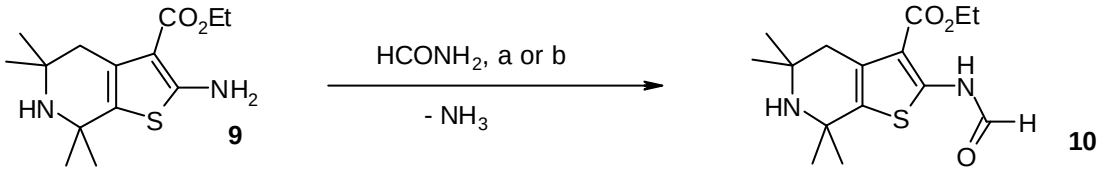
Scheme 2.

These results can be summarized by the following, experimentally proved reaction course (Scheme 3).



Scheme 3.

When, instead of the amino nitrile (**1**), the corresponding ethyl ester (**9**)[1] was heated in formamide, no ring transformation was observed (Scheme 4).

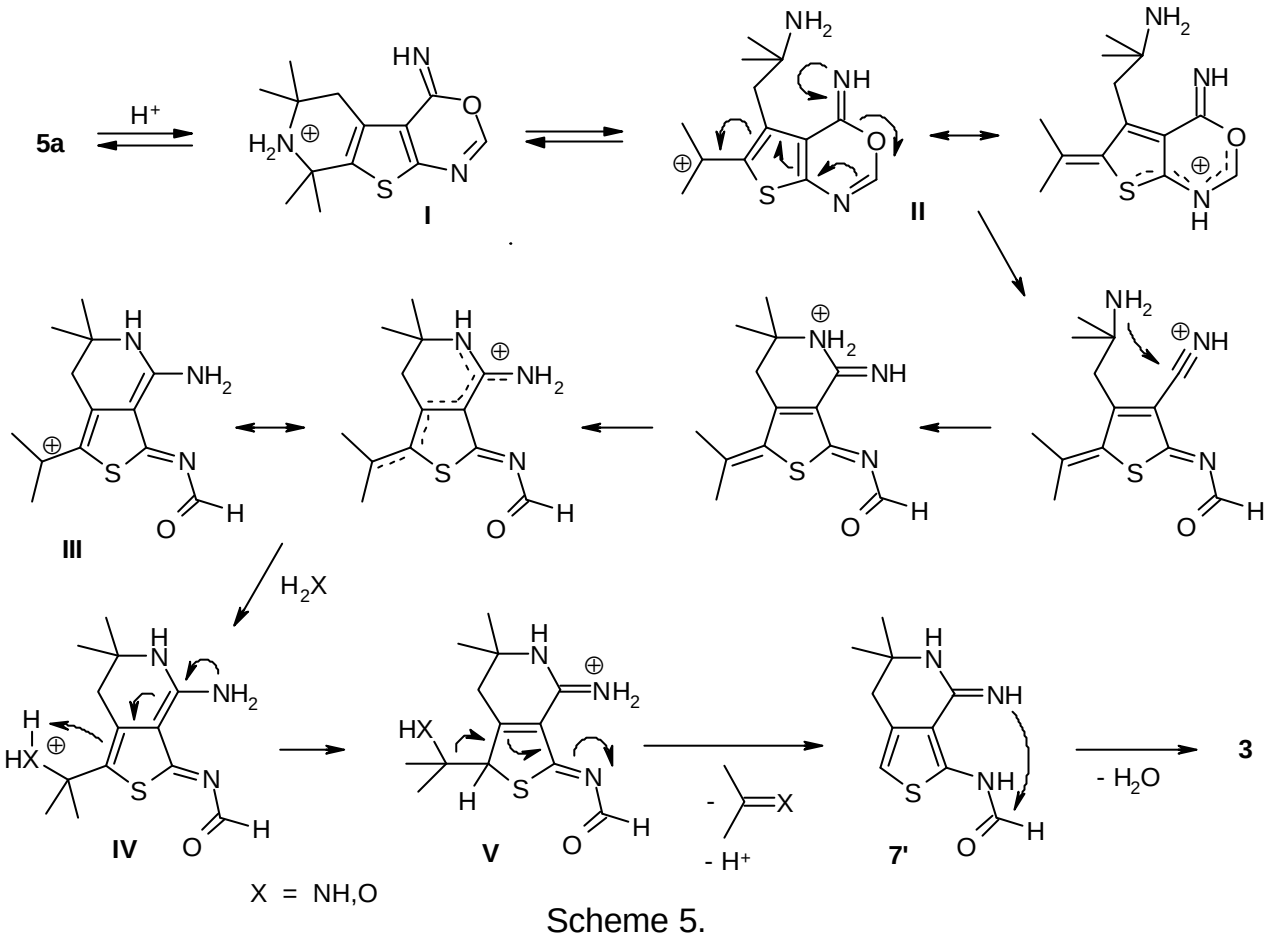


a: 140-160°C, 30 min, 19% by ^{1}H NMR; b: 185°C, 2 h, 51% by GC-MS

Scheme 4.

Consequently, the opening of the tetrahydropyridine ring of **5** is not simply the result of high steric strain but must be related to the cyano group. The following hypothetical mechanism might be an explanation of all the observed features of this cascade reaction (Scheme 5). According to this hypothesis, the initially formed thienylformamide (**5a**) is in equilibrium with a thienooxazine derivative formed by nucleophilic attack of the amide oxygen at the cyano carbon followed by tautomerization. The thienooxazine is in equilibrium with its protonated form (**I**). The partial, reversible formation of the protonated thienooxazine (**I**) strongly promotes the cleavage of the "piperidine" ring because the resulting cation (**II**) is stabilized by delocalization of the positive charge over the aromatic system to the oxygen atom. So far, the whole reaction is reversible. When the oxazine ring of the cation (**II**) is opened the resulting protonated cyano group is attacked by the primary amino group. Tautomerization of the resulting amidinium ion gives the resonance-stabilized carbenium-amidinium ion (**III**). This cation is reactive enough to be attacked by every nucleophile present in the mixture, certainly ammonia or even traces of water from the non-dried solvent, to give the cation (**IV**). The latter one contains a vinylogous enamine structure. So an intramolecular proton transfer from the ammonium or oxonium atom to the neighboring highly nucleophilic thiophene carbon occurs. Structure (**V**) is now striving for re-establishing an aromatic thiophene ring. This is achieved by cleavage of a carbon-carbon bond with release of acetone or acetone imine to give, after tautomerization and deprotonation, the real intermediate (**7'**). This release of acetone or its imine is formally comparable with a retro-aldol reaction, and its driving force might be the formation of two

thermodynamically more stable products from **V**. Finally, cyclization of the bicyclic amidine (**7'**) affords the tricycle (**3**) (Scheme 5). Depending on the conditions, the essential protons can come from the protic solvent, formamide, or from decomposing ammonium acetate.

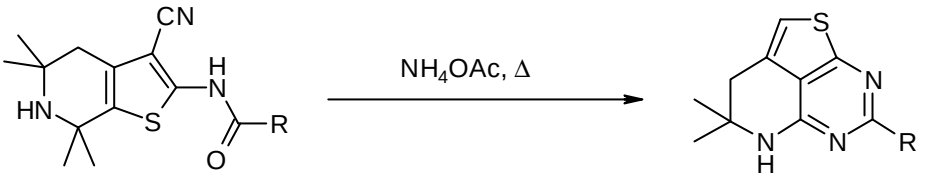


Scheme 5.

All reactions outlined in Scheme 5, except the last step (**7'** → **3**), are hypothetical. However, this mechanism is supported by the above-mentioned results.

PREPARATIVE ASPECTS

7-Substituted derivatives of the new ring system are easily available by heating of the corresponding thienylamides (**5**) with ammonium acetate in a protic amide as solvent (Scheme 6). Ammonium acetate promotes the reaction while it is decomposing into acetic acid (the proton source necessary for the condensation steps) and ammonia (a nucleophile probably promoting the removal of the isopropylidene group according to Scheme 5). This synthesis can be considered as a short and generally applicable method, since thienylamides (**5**) derived from **1** are available from both carboxylic anhydrides and carboxylic acid chlorides by selective acylation of the 2-amino group.[1] The new thienylamides (**5a**) and (**5c**) were prepared in analogy with the previously reported[1] examples.

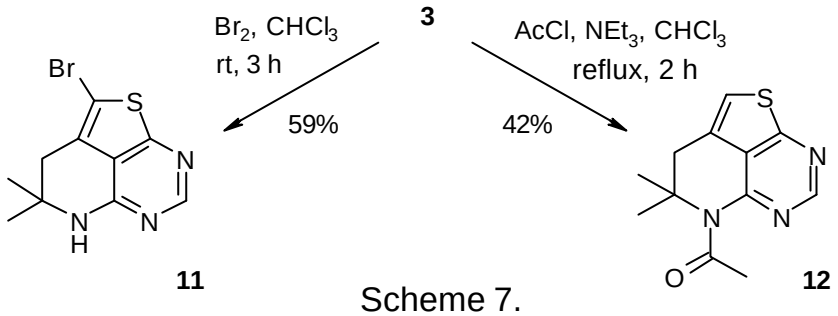


R = H	**5a**	$HCONH_2$ or NMA, 140°C, 2-4 h, up to 93%[a)]	**3**
R = Me	**5b**	NMA, 140°C, 90 min, 42%[b)]	**6**
R = Ph	**5c**	NMA, 185°C, 1 h, 56%[b)]	**8**

[a)] GC-MS; [b)] isolated yield; NMA = *N*-methylacetamide

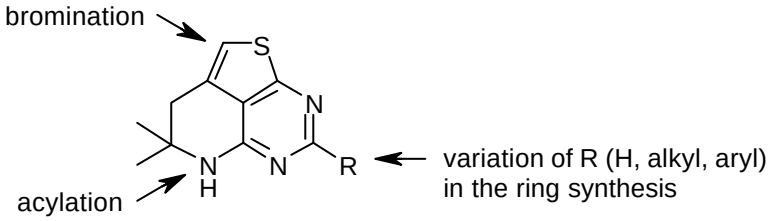
Scheme 6.

Finally, the brominated derivative (**11**) and the acetylated compound (**12**) were prepared from **3** (Scheme 7). The position of the acetyl group of compound (**12**) was confirmed by $^{1}H/^{15}N$ correlated NMR experiments. Thus, the ^{15}N signal of the sp^3 hybridized nitrogen showed a coupling with the methyl and methylene protons of the dihydro-1*H*-pyridine ring.



Scheme 7.

In summary, an unusual cascade-like ring transformation was mechanistically explained and shown to be a preparatively useful method to obtain novel heterocycles. The new ring system can be modified at three positions.



EXPERIMENTAL

NMR spectra were recorded on Bruker AC-200 P (200 MHz for ^{1}H, 50 MHz for ^{13}C), Bruker AC-300 P (300 MHz for ^{1}H, 75 MHz for ^{13}C) and Bruker DRX-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C, 50 MHz for ^{15}N), respectively. Chloroform and dimethyl sulfoxide, respectively, were used as internal standards for ^{1}H and ^{13}C NMR spectra. ^{13}C peaks were assigned by means of DEPT spectra. For the ^{15}N NMR spectra, nitromethane was used as an external standard. IR spectra were recorded on a Nicolet 205 FT-IR

spectrometer. GC-MS were recorded on a Hewlett Packard GC-MS device (5890 Series II, EI, 70 eV, quadrupole) with IR detector (HP 5965B, 550-4000 cm^{-1}). Elemental analyses were performed on a Carlo Erba CHN-S Elemental Analyzer 1108. The syntheses of compounds (**1**, **4**, **5b** and **9**) were described previously.[1]

4,4-Dimethyl-4,5-dihydro-3*H*-thieno[2',3',4'-*de*]pyrido[2,3-*d*]pyrimidine (3). A suspension of aminothiophene (**1**) (4.71 g, 20.0 mmol) in formamide (30 mL) was stirred at 180°C for 1 h. After cooling to rt, filtration and washing with water and little ethanol afforded 3.12 g (76%) of spectroscopically pure **3** as brownish crystals; mp 198-201°C. An analytical sample was recrystallized from ethylacetate/ethanol (1:1) to give pale yellow crystals; mp 201-202°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.37 (s, 6H, 4-Me), 2.86 (d, 2H, *J* = 1 Hz, CH_2), 6.69 (br s, 1H, NH), 6.84 (t, 1H, *J* = 1 Hz, 2-H), 8.48 (s, 1H, 7-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.6 (4-Me), 38.5 (C-3), 53.9 (C-4), 115.8 (C-8b), 116.3 (C-2), 127.5 (C-2a), 154.9 (C-7), 157.3 (C-5a), 164.0 (C-8a); ^{13}C GD NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ = 27.1 (qq, *J* = 125 Hz and 4 Hz, 4-Me), 37.3 (tm, *J* = 130 Hz, C-3), 52.4 (m, C-4), 114.3 (dt, *J* = 185 Hz and 4 Hz, C-2), 114.3 (m, C-8b), 126.6 (td, *J* = 6 Hz and 3.5 Hz, C-2a), 154.2 (d, *J* = 200 Hz, C-7), 156.3 (d, *J* = 10 Hz, C-5a), 162.5 (dd, *J* = 14 Hz and 7.5 Hz, C-8a); MS: *m/z* (%) = 207 (3), 206 (10), 205 (65) [M^+], 204 (63), 191 (12), 190 (100) [M^+ - CH_3], 175 (43), 45 (11), 39 (11); Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47; S, 15.62. Found: C, 58.70; H, 5.52; N, 20.49; S, 15.43.

***N*-(3-Cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl)formamide (5a).** The following formylation procedure was adopted from a reported example.[3] In a 250 mL two-necked flask with reflux condenser, a mixture of anhydrous formic acid (50 mL) and acetanhydride (50 mL) was stirred at 50-60°C oilbath temperature for 2 h. After removal of the oilbath, solid aminothiophene (**1**) (14.1 g, 60 mmol) was added and the mixture was stirred at 60°C for 40 min. The mixture was poured carefully into ice water (500 mL) and filtered through a hard paper filter. To the resulting clear filtrate, 40% sodium hydroxide and solid sodium carbonate were added under cooling to adjust to pH 10-11. After 15 min, the precipitate was collected by filtration and washed with water to give 12.8 g (59%) of **5a** as pale reddish crystals; mp 194-197°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz): δ = 1.12 (s, 6H, 5-Me), 1.35 (s, 6H, 7-Me), 2.36 (s, 2H, CH_2), 8.30 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz): δ = 28.2 (5-Me), 32.3 (7-Me), 35.6 (C-4), 48.5 (C-5), 50.5 (C-7), 91.9 (C-3), 112.6 (nitrile), 127.1 (C-3a), 133.8 (C-7a), 144.3 (C-2), 157.0 (C=O); MS: *m/z* (%) = 263 (0.3) [M^+], 249 (15), 248 (100) [M^+ - CH_3], 220 (13), 178 (11), 163 (8); Anal. Calcd for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96; S, 12.17. Found: C, 58.63; H, 6.46; N, 15.51; S, 12.08.

***N*-(3-Cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl)benzamide (5c).** To a stirred mixture of aminothiophene (**1**) (1.18 g, 5.0 mmol), dry acetonitrile (10 mL) and *N*-methylpiperidine

(1.82 mL, 15 mmol), a solution of 1.55 g (11.0 mmol) of benzoyl chloride in dry acetonitrile (2 mL) was added dropwise. The mixture was refluxed for 7 h. The solvent was evaporated off, and the resulting black residue was treated with water (50 mL), acidified with glacial acetic acid and stirred intensively for 10 min. Precipitated oily impurities were removed by decantation and the aqueous solution was treated with sodium carbonate until pH~9 and extracted with dichloromethane. The solvent was evaporated. The residue was dissolved in ethanol (20 mL) and stirred with freshly powdered sodium hydroxide (0.60 g, 15 mmol) at 50°C for 1 h, in order to cleave the intermediate dibenzoylimide.[1] Ethanol was evaporated off and the residue dissolved in water (50 mL). After filtration, glacial acetic acid was added dropwise to the stirred filtrate to adjust to pH~10. The resulting precipitate was collected and washed with water to give 0.93 g (55%) of crude benzamide (**5c**) as a brownish solid; mp 149-156°C. An analytical sample was recrystallized from acetonitrile to give pure **5c** as pale brownish crystals; mp 159-161°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.21 (s, 6H, 5-Me), 1.48 (s, 6H, 7-Me), 2.47 (s, 2H, CH_2), 7.50-7.64 (m, 3H, Ph 3-/ 4-/5-H), 7.92 (d, 2H, *J* = 7.5 Hz, Ph 2-/6-H), 9.09 (br s, 1H, CO-NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.9 (5-Me), 34.0 (7-Me), 37.6 (C-4), 50.3 (C-5), 52.3 (C-7), 93.9 (C-3), 114.4 (nitrile), 127.4 (Ph C-2/C-6), 128.6 (C-3a), 129.1 (Ph C-3/C-5), 131.8 (C-7a), 133.0 (Ph C-4), 136.3 (Ph C-1), 147.4 (C-2), 163.6 (C=O); Anal. Calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38; S, 9.45. Found: C, 66.68; H, 6.24; N, 12.11; S, 8.87.

4,4,7-Trimethyl-4,5-dihydro-3*H*-thieno[2',3',4'-*de*]pyrido[2,3-*d*]pyrimidine (6). A mixture of amide (**5b**)[1] (0.554 g, 2.00 mmol), *N*-methylacetamide (3 mL) and non-dried ammonium acetate (0.31 g, < 4 mmol) was stirred at 140°C for 90 min. After cooling, the solution was treated with water (25 mL) and sodium carbonate to adjust to pH~10-11. From the resulting emulsion, extraction with dichloromethane, washing with water, drying with sodium sulfate and evaporation gave crude **6** impured with about 20% **5b** (^{1}H NMR). The crude product was dissolved in ether (5 mL) and extracted with 1M aqueous sodium hydroxide (2×10 mL). Separation of the organic layer, addition of ether (15 mL), drying with potassium carbonate and evaporation afforded 0.184 g (42%) of **6** as a pale yellowish solid; mp 103-104°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.21 (s, 6H, 4-Me), 2.42 (s, 3H, 7-Me), 2.75 (s, 2H, 3-H), 6.99 (s, 1H, 2-H), 7.72 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 25.7 (7-Me), 27.7 (4-Me), 37.9 (C-3), 53.1 (C-4), 112.8 (C-8b), 114.3 (C-2), 127.5 (C-2a), 157.1 (C-5a), 163.8/164.2 (C-7/C-8a); MS: *m/z* = 220 (13), 219 (72) [M^+], 218 (68), 189 (31), 205 (14), 204 (100), 42 (11); Anal. Calcd for $C_{11}H_{13}N_3S$: C, 60.24; H, 5.98; N, 19.16; S, 14.62. Found: C, 60.55; H, 6.09; N, 19.12; S, 14.51.

***N*1-(4-Imino-6,6-dimethyl-4,5,6,7-tetrahydrothieno[3,4-*c*]pyridin-3-yl)benzamide (7).** A mixture of amide (**5c**) (0.271 g, 0.80 mmol), formamide (2 mL) and non-dried ammonium acetate (0.08 g, < 1 mmol) was stirred at 140°C for 2 h. After cooling, the resulting suspension was treated with water and sodium

carbonate to adjust to pH~9. The precipitate was collected, washed with water and dried. The crude product was suspended in dichloromethane (10 mL), stirred for 20 min, collected by filtration and washed with dichloromethane to give 0.159 g (67%) of amidine (**7**) as a greenish-yellow solid; mp 280-290°C (decomp); ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.26 (s, 6H, Me), 2.70 (s, 2H, CH_2), 6.31 (s, 1H, 1-H), 7.40-7.44 (m, 3H, Ph 3-/4-/5-H), 7.66 (br s, 1H, 5-H), 8.05 (d, 2H, *J* = 8 Hz, Ph 2-/6-H), 8.27 (s, 1H, C=NH), 10.42 (br s, 1H, CO-NH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 27.7 (Me), 37.5 (C-7), 52.9 (C-6), 102.3 (C-3a), 108.3 (C-1), 127.9/128.0 (Ph C-2,-6/C-3,-5), 129.0 (C-7a), 130.0 (Ph C-4), 138.8 (Ph C-1), 157.2 (C=NH), 164.6 (C-3), 169.5 (C=O), peak assignment by means of a ^{1}H/^{13}C HMBC 2D NMR spectrum; ^{1}H/^{15}N HSQC 2D NMR [DMSO-d_6, SF(^{1}H) = 500 MHz, SF(^{15}N) = 50 MHz, 256 experiments in F1 (^{15}N axis), 59.4 Hz/Pt resolution in F1, 4.9 Hz/Pt resolution in F2 (^{1}H axis)]:

δ (ppm)	10.42 (N<u>H</u>-CO)	8.27 (C=N<u>H</u>)	7.66 (5-H)
-289.6 (N-5)			x
-289.4 (<u>N</u>H-CO)	x		
-263.1 (C=<u>N</u>H)		x	

IR (KBr): 3388/3242/3150 cm^{-1} (NH), 3081 (=CH), 2966 (CH), 1641 (C=N), 1580, 1491, 1454, 1436, 1387, 1361, 702; GC-IR-MS (column DB-5 MS, 30m×0.25mm×0.30µm, injection on column, 50°C →300°C): t_r (min) = 18.2-19.5 (broad, 100%), IR at 18.2 min and MS at 18.9 min identical with spectra of compound (**8**); Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04; S, 10.71. Found: C, 63.79; H, 5.71; N, 13.83; S, 10.46.

4,4-Dimethyl-7-phenyl-4,5-dihydro-3*H*-thieno[2',3',4'-*de*]pyrido[2,3-*d*]pyrimidine (8). A mixture of amide (**5c**) (0.204 g, 0.6 mmol), *N*-methylacetamide (1.5 mL) and non-dried ammonium acetate (0.11 g, < 1.4 mmol) was stirred at 185°C for 1 h. After cooling, the solution was treated with water (25 mL) and sodium carbonate to adjust to pH~9. The resulting precipitate was collected and washed with water to give a brownish-gray solid. This was dissolved in ether (2 mL) and purified on aluminium oxide (30 g, Alox neutral, activity level I, Chemiewerk Greiz-Döhlau) by elution with *n*-pentane/ether (1:1) to give 0.095 g (56%) of **8** as colorless crystals; mp 158-160°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.31 (s, 6H, 4-Me), 2.86 (s, 2H, CH_2), 5.41 (br s, 1H, NH), 6.81 (s, 1H, 2-H), 7.42-7.47 (m, 3H, Ph 3-/4-/5-H), 8.41 (dd, 2H, *J* = 6 Hz and 2 Hz, Ph 2-/6-H); ^{13}C NMR ($CDCl_3$, 75 Hz): δ = 28.8 (4-Me), 38.8 (C-3), 54.2 (C-4), 114.5 (C-8b), 116.1 (C-2), 127.4 (C-2a), 128.3 (Ph C-2/C-6 and Ph C-3/-5 overlapped), 129.9 (Ph C-4), 138.8 (Ph C-1), 157.4 (C-5a), 162.2/165.6 (C-7/C-8a); IR (GC): 3415 cm^{-1} (NH), 3074 (=CH), 2974 (CH), 1586, 1437, 1325; MS: *m/z* (%) = 282 (16), 281 (77) [M^+], 280 (52), 267 (19), 266 (100) [M^+ - CH_3], 251 (25), 133 (21), 104 (18), 77 (24); Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93; S, 11.39. Found: C, 68.26; H, 5.52; N, 14.80; S, 11.06.

2-Bromo-4,4-dimethyl-4,5-dihydro-3*H*-thieno[2',3',4'-*de*]pyrido[2,3-*d*]pyrimidine (11). To a stirred solution of tricycle (**3**) (0.62 g, 3.0 mmol) in chloroform (20 mL), a solution of bromine (0.15 mL, 3 mmol) in chloroform (10 mL) was dropped over 1 h. The mixture was stirred for another 2 h at rt. After evaporation of the solvent, the solid residue was treated with 10% sodium carbonate solution. The resulting precipitate was collected and recrystallized from ethyl acetate/ethanol (1:1) to give 0.50 g (59%) of **11** as white crystals; mp 253-255°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ = 1.27 (s, 6H, Me), 2.65 (s, 2H, CH_2), 7.55 (br s, 1H, NH), 8.26 (s, 1H, 7-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.8 (Me), 37.8 (CH_2), 54.0 (C-4), 106.6 (C-2), 116.1 (C-8b), 127.7 (C-2a), 155.3 (C-7), 155.8 (C-5a), 164.3 (C-8a); IR (KBr): 3445 cm^{-1} (NH), 3215, 3162, 3089 (=CH), 2971 (CH), 1597, 1533, 1398; MS: *m/z* (%) = 286 (12), 285 (72) [M^+], 284 (66), 283 (72) [M^+], 282 (60), 270 (96) [M^+ - CH_3], 269 (16), 268 (100) [M^+ - CH_3], 255 (43), 253 (44), 189 (66), 188 (14), 94 (28), 39 (14); Anal. Calcd for $C_{10}H_{10}N_3BrS$: C, 42.26; H, 3.55; N, 14.79; S, 11.28; Br, 28.12. Found: C, 42.53; H, 3.64; N, 14.82; S, 11.10; Br, 27.71.

1-(4,4-Dimethyl-4,5-dihydro-3*H*-thieno[2',3',4'-*de*]pyrido[2,3-*d*]pyrimidin-5-yl)-1-ethanone (12). Triethylamine (10.5 mL, 75 mmol) was added to a solution of tricycle (**3**) (3.08 g, 15.0 mmol) in chloroform (50 mL). With stirring and water cooling, acetyl chloride (4.3 mL, 60 mmol) was added dropwise over 10 min. The mixture was refluxed for 2 h. After evaporation of the solvent, the resulting oily residue was stirred intensively with a mixture of *n*-pentane (50 mL), ether (50 mL) and triethylamine (3.0 mL, 21.4 mmol) for 30 min. The resulting brown precipitate was collected and suspended in water (30 mL). Filtration and drying gave 2.20 g (59%) of crude **12**. This was dissolved in acetonitrile (200 mL). After filtration, water and ice were added to the filtrate until a total volume of about 750 mL. After 30 min, the resulting crystals were collected and washed with water to give 1.54 g (42%) of pure **12** as light brown crystals; mp 167-169°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.50 (s, 6H, 4-Me), 2.63 (s, 3H, Me-CO), 2.97 (d, 2H, *J* = 1.3 Hz, CH_2), 6.97 (t, 1H, *J* = 1.3 Hz, 2-H), 8.69 (s, 1H, 7-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.6 (4-Me), 29.3 (Me-CO), 41.5 (C-3), 61.3 (C-4), 117.5 (C-2), 117.7 (C-8b), 126.5 (C-2a), 154.3 (C-7), 155.1 (C-5a), 166.2 (C-8a), 175.8 (C=O); ^{1}H/^{15}N HMBC 2D NMR [$CDCl_3$, SF(^{1}H) = 500 MHz, SF(^{15}N) = 50 MHz, 300 experiments in F1 (^{15}N axis), 67.6 Hz/pt resolution in F1, 3.7 Hz/Pt resolution in F2 (^{1}H axis)]:

δ (ppm)	8.69 (7-H)	6.97 (2-H)	2.97 (CH_2)	2.63 (Me-CO)	1.50 (4-Me)
-225.0 (N-CO)			x	x	x
-133.4 (N-6)	x			x	
-124.7 (N-8)	x	x			

MS: *m/z* (%) = 247 (12) [M^+], 206 (7), 205 (46), 204 (42), 191 (12), 190 (100), 175 (18), 43(10); Anal. Calcd for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 17.00; S, 12.96. Found: C, 58.33; H, 5.36; N, 17.04; S, 12.73.

REFERENCES

1. U. Sensfuss and W. D. Habicher, *Heteroatom Chem*., 1998, **9**, 529.
2. E. C. Taylor and M. C. Killop, 'Advances in Organic Chemistry: Methods and Results, Vol. 7: The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles', ed. by E. C. Taylor, Interscience Publishers, New York, 1970, pp. 219-374.
3. F. Johannsen, A. Jørgensen, and E. B. Pedersen, *Chem. Scr*., 1986, **26**, 347.

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