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2-Aminothiophenes from Triacetonamine: A Convenient Way to Novel Sterically Hindered Piperidine Derivatives

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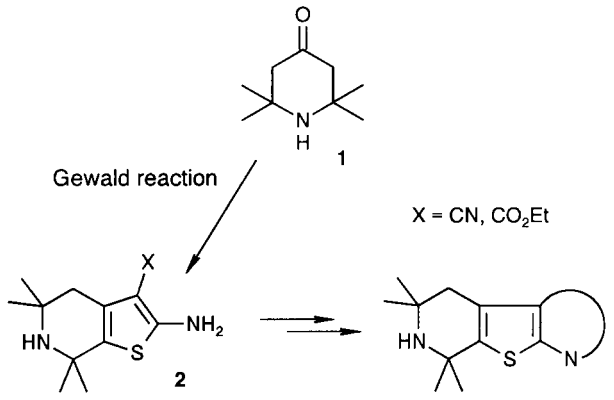
ABSTRACT: *Bicyclic 2-aminothiophenes* **2**, *which are available by the Gewald reaction of 2,2,6,6-tetramethyl-4-piperidone (triacetonamine,* **1***), were employed in cyclizations to give new tricyclic thienopyridine and thienopyrimidine derivatives, without protection of the piperidine nitrogen, whereas methylation of* **2** *occurred exclusively at the piperidine nitrogen. Acylation of* **2** *in the presence of a tertiary amine yielded N-thienyl imides, due to the high NH acidity of the intermediate N-thienyl amides. Similarly, benzylation of an N-thienyl amide proceeded readily in sodium ethoxide solution.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:529–536, 1998

Sterically hindered amines derived from 2,2,6,6-tetramethylpiperidine are well known to be important in several fields. They are used as precursors for spin labels [1] and for highly efficient light stabilizers [2]. Some compounds of this type have physiological effects such as antitumor activity, analgesic, antipyretic, and anticholinergic action [3,4]. Hence, there is a considerable interest in obtaining novel multifunctional compounds bearing a sterically crowded piperidine function. Triacetonamine (2,2,6,6-tetramethyl-4-piperidone, **1**) is the most common starting material for 2,2,6,6-tetramethylpiperidine derivatives. Generally, **1** can be modified at the carbonyl group without difficulties. In the literature, however, there are only a few examples of reactions of **1** at the carbon C-3, presumably due to steric hindrance [4].

As for the biological activity, it should be of interest to combine the piperidine function of **1** with pyridine- and pyrimidine-type structures that are known to have biological effects. Our idea is outlined in Scheme 1. The first step of this approach is a Gewald reaction [5] with **1**. This reaction of enolizable ketones with CH-acidic nitriles and sulfur is a well-established method for the synthesis of biologically active compounds and dyes [6]. The resulting 2-aminothiophene-3-carboxylic acid derivatives **2** should be able to fuse with several heterocyclic structures by electrophilic attack on the primary 2-amino group followed by intramolecular cyclization with



SCHEME 1

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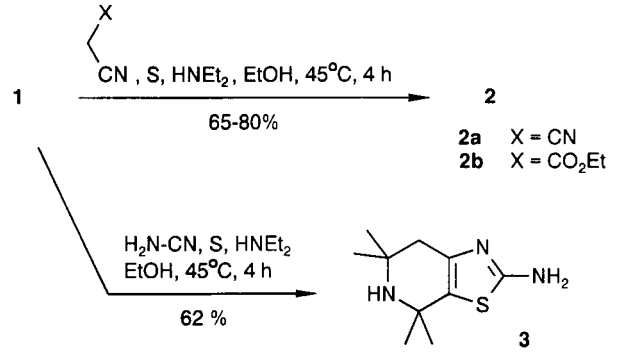
the acceptor group X at the 3-position (Scheme 1). However, the aliphatic piperidine nitrogen in **2** should be expected to be more nucleophilic than the primary amino group, in spite of the steric hindrance, so that the possibility of a competitive electrophilic attack on the piperidine nitrogen followed by an opening of the strained tetramethylpiperidine ring should be taken into consideration. The goal of our work was therefore to investigate the reaction behavior of the aminothiophene derivatives **2** in acylations and anellations.

Gewald reactions with 4-piperidones have been reported [7], but not with triacetonamine (**1**). By employing **1** in the reaction with sulfur and malononitrile or ethyl cyanoacetate, we obtained the expected bicyclic aminothiophenes **2** in satisfactory yields [8] (Scheme 2). A similar cyclocondensation of **1** with cyanamide and sulfur yielded the corresponding aminothiazole **3** [9], according to a method reported for simple aliphatic ketones [10]. However, these results cannot be extended to *N*-substituted derivatives of **1**. Thus, the reaction of 1,2,2,6,6-pentamethyl-4-piperidone (*N*-methyltriacetonamine) with sulfur and malononitrile or ethyl cyanoacetate under Gewald reaction conditions resulted in a mixture containing the corresponding aminothiophenes **4** besides several unidentified products. The thiophenes **4** were detected by GC-MS in a proportion of 40 to 60%. In order to explain this result, several reasons may be discussed. The pentamethylpiperidone ring is more sterically strained and shows a higher tendency to opening than the tetramethyl compound **1** [11]. On the other hand, the shielding effect of the methyl groups on the carbon C-3 might be stronger in the pentamethyl system [12]. This effect would slow down the thiolation step of the Gewald reaction and hence promote side reactions, especially the dimerization of the CH-acidic nitrile.

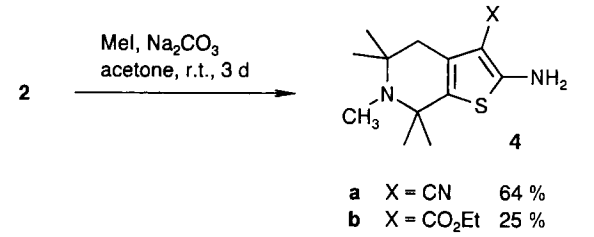
Due to the above-mentioned difficulties with the Gewald reaction of 1,2,2,6,6-pentamethyl-4-piperidone, we prepared the pentamethylpiperidine derivatives **4** by methylation of the tetramethyl compounds **2**. Methylation of **2a** and **2b** with methyl iodide occurs nearly exclusively at the piperidine nitrogen as expected. Consequently, this is the method of choice to obtain **4** (Scheme 3).

We synthesized the novel tricyclic thienopyrimidine and pyridine derivatives **6–7** starting from the aminothiophenes **2**, according to known examples of cyclizations with *ortho*-amino carboxylic acid derivatives. For the preparation of the thienopyrimidine derivatives **6a** and **6b**, we used methods reported by Taylor and Berger [13] and Gewald and Martin [14]. The new tricyclic thienopyridone **7** was prepared by reacting the aminonitrile **2a** with ethyl cyanoacetate and sodium ethoxide. By changing the literature procedure [15] for this reaction, the product was separated directly as the sodium salt from the ethanolic reaction mixture. Afterwards, **7** was precipitated from water at pH 9 (Scheme 4).

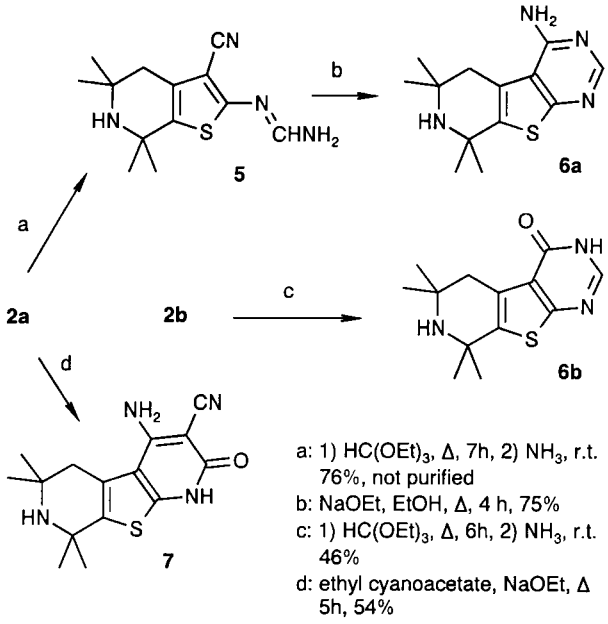
As indicated by these examples (Scheme 4), the



SCHEME 2



SCHEME 3

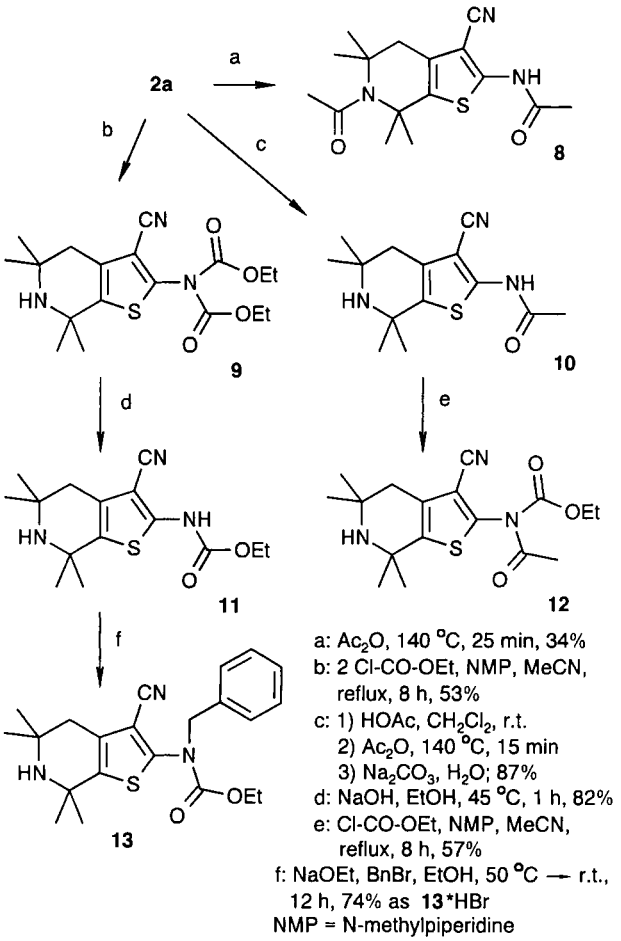


SCHEME 4

initial attack of the electrophiles triethyl orthoformate or ethyl cyanoacetate upon **2** occurs mainly at the primary amino group but not at the piperidine nitrogen, which is in contrast to the methylation of **2** described earlier. The driving forces for the preferential attack at the NH_2 group are presumably the steric hindrance at the tetramethylpiperidine nitrogen as well as the thermodynamic stability of the reaction products since the *N*-substituent's double bond can conjugate with the thiophene π-system.

N-Acetylations of 2-aminothiophenes with acetic anhydride are known in the literature [16]. Since the acylation-analogous reactions of **2** with ethyl cyanoacetate or triethyl orthoformate occurred at the primary amino group (Scheme 4) with reversed selectivity as compared to methylation (Scheme 3), we investigated acylations of the aminocyano-thiophene **2a** with acetic anhydride and ethyl chloroformate (Scheme 5).

Refluxing **2a** in acetic anhydride gave the diamide **8** in 34% yield, along with a small amount of the amide **10**. The low yield of diamide **8** may be explained by a possible cleavage of the piperidine ring of **8** resulting in products soluble in acetic anhydride. However, the monoamide **10** could be prepared from **2a** in high yield after protonation of the basic piperidine nitrogen with glacial acetic acid. Reaction of **2a** with ethyl chloroformate and a tertiary amine did not give the urethane **11** but the imide **9**, even when equimolar amounts of **2a** and ethyl chloroformate were used. Obviously, after formation of the urethane **11**, it is deprotonated by the basic amine, and the resulting urethane anion is acylated again to give the imide **9**. Acylation of **2a** with ethyl chloroformate at the piperidine nitrogen was not observed, and it seems to be impeded by steric effects. Compound **9** can be handled in weakly acidic or neutral aqueous solutions without hydrolysis but not in strongly alkaline solutions. It was crystallized as a hydrate from aqueous solution at pH range 7–8. The imide **9** was readily transformed to the urethane **11** by treatment with sodium hydroxide. Analogously to the formation of **9**, heating of the acetamide **10** with ethyl chloroformate and *N*-methylpiperidine in acetonitrile gave the imide **12**. Because a direct *N*-alkylation of 4,5-dialkyl substituted Gewald-type aminothiophenes is difficult according to the literature [17] and to the methylation results mentioned earlier (Scheme 3), the NH acidity of the amides **10** and **11** was expected to be advantageous for the introduction of alkyl substituents. In fact, *N*-alkylation of the urethane **11** with benzyl bromide proceeded readily in sodium ethoxide solution to give the *N*-benzyl urethane **13** (Scheme 5).



SCHEME 5

In summary, with the Gewald reaction of **1**, a convenient way to novel 2,2,6,6-tetramethylpiperidine derivatives is opened because the resulting aminothiophenes **2** are shown to be useful in combining a sterically hindered amine function with heteroaromatic structures by short synthetic routes in moderate yields. *N*-Thienyl imides (**9** and **12**) are described for the first time. The 2-amidothiophene-3-carbonitriles **10** and **11** have been found to be deprotonated even by comparatively weak bases; the resulting new diacylation and *N*-benzylation procedures are supposed to be generally applicable to 2-aminothiophene-3-carboxylic acid derivatives.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 200 MHz, and ^{13}C NMR spectra were recorded at 50 MHz (Bruker AC-200P) in $CDCl_3$ or DMSO with TMS as internal standard. Chemical shifts are expressed in parts per million. ^{13}C peaks were assigned by means of DEPT (distortionless enhancement by polarization transfer) or GD (gated decoupling), respectively. GC-MS was performed on a Hewlett Packard device (5890

Series II, EI, 70 eV, quadrupole). Elemental analyses were performed on a Carlo Erba CHN-S Elemental Analyzer 1108.

2-Amino-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carbonitrile (**2a**). Diethylamine (60 mL) was added to a stirred mixture of triacetonamine (**1**) monohydrate (103.8 g, 600 mmol), malononitrile (40 g, 600 mmol), sulfur (19.2 g, 600 mmol), and EtOH (260 mL). Stirring was continued for 4 hours at 45°C. After mixing with H_2O (800 mL), the dark reaction mixture was left to stand in a refrigerator for 3 days. The resulting precipitate was collected by filtration and washed with H_2O to give 110.9 g (78%) of spectroscopically pure **2a** as a brownish solid; mp 192–195°C. An analytical sample was recrystallized from EtOH to afford beige crystals; mp 194–195°C; ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 6H, 5-Me), 1.39 (s, 6H, 7-Me), 2.39 (s, 2H, CH_2), 4.49 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 29.2 (5-Me), 32.7 (7-Me), 37.2 (C-4), 49.4 (C-5), 51.7 (C-7), 85.0 (C-3), 115.4 (nitrile), 125.5 (C-7a), 128.3 (C-3a), 161.7 (C-2); MS: *m/z* (%) 235 (3) [M^+], 222 (5), 221 (13), 220 (100), 203 (9), 188 (3), 178 (13), 163 (8), 42 (10); $C_{12}H_{17}N_3S$ (235.34) calcd: C, 61.24, H, 7.28, N, 17.86, S, 13.62. Found: C, 61.08, H, 7.11, N, 17.72, S, 13.59.

Ethyl 2-Amino-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylate (**2b**). The same procedure as described for **2a** was performed starting with **1** hydrate (34.6 g, 200 mmol), ethyl cyanoacetate (22.6 g, 200 mmol), sulfur (6.4 g, 200 mmol), diethylamine (20 mL), and EtOH (50 mL) to give 48.8 g (86%) of spectroscopically pure **2b** as light brown crystals; mp 109–112°C. An analytical sample was recrystallized from *n*-hexane/$CHCl_3$ (4:1) to give brownish crystals; mp 111–113 °C; ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 6H, 5-Me), 1.32 (t, 3H, J = 7.1 Hz, ester Me), 1.36 (s, 6H, 7-Me), 2.58 (s, 2H, 4-CH_2), 4.28 (q, 2H, J = 7.1 Hz, O–CH_2), 6.00 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 14.4 (ester Me), 30.2 (5-Me), 33.7 (7-Me), 40.3 (C-4), 50.0 (C-5), 51.7 (C-7), 59.3 (O–CH_2), 105.5 (C-3), 125.6 (C-7a), 129.7 (C-3a), 162.1 (C-2), 165.9 (C=O); MS: *m/z* (%) 282 (4) [M^+], 269 (6), 268 (16), 267 (100), 221 (62), 205 (11), 179 (16), 103 (7), 42 (9), 29 (13); $C_{14}H_{22}N_2O_2S$ (282.39) calcd: C, 59.54; H, 7.85; N, 9.92; S, 11.35. Found: C, 59.60, H, 7.93, N, 9.95, S, 11.39.

2-Amino-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thiazolo[2,3-c]pyridine (**3**). Diethylamine (10 mL) was added dropwise to a stirred mixture of **1** (15.5 g, 100 mmol), cyanamide (4.2 g, 100 mmol), sulfur (3.2 g, 100 mmol), and abs. EtOH (20 mL). After having been stirred for another 3 hours at 40°C, the mixture was poured into H_2O (150 mL) and acidified by aqueous HCl. After filtration, the dark brownish-red filtrate was extracted with ether (3 × 100 mL). The acidic aqueous phase was treated with NaOH and Na_2CO_3 to adjust to pH 11–12. The precipitate formed was collected by filtration to give 13.1 g (62%) of pure **3** as a colorless solid; mp 219–221°C; ^{1}H NMR (DMSO-d_6): δ 1.10 (s, 6H, 7-Me), 1.28 (s, 6H, 5-Me), 2.24 (s, 2H, 4-CH_2), 6.64 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 29.8 (7-Me), 33.4 (5-Me), 39.1 (C-4), 50.5/51.6 (C-5/C-7), 122.3 (C-7a), 142.4 (C-3a), 165.9 (C-2); $C_{10}H_{17}N_3S$ (211.32) calcd: C, 56.83, H, 8.11, N, 19.89, S, 15.17. Found: C, 56.98, H, 8.07, N, 19.72, S, 15.11.

2-Amino-5,5,6,7,7-pentamethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carbonitrile (**4a**). A solution of **2a** (1.18 g, 5.0 mmol) in acetone (20 mL) was stirred with Na_2CO_3 (4 g). After addition of MeI (0.9 mL, about 15 mmol), the flask was closed and the mixture stirred vigorously for 3 days at room temperature. After removal of the solids and evaporation of the solvent at room temperature, the brown residue was treated with EtOH (2 mL) and H_2O (30 mL), and the mixture was stirred for 15 minutes. The resulting precipitate was collected and recrystallized from *n*-hexane/$CHCl_3$ (6:1) to give 0.80 g (64%) of pure **4a** as a brownish solid; mp 159–161°C; ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 6H, 5-Me), 1.34 (s, 6H, 7-Me), 2.35 (s, 3H, N-Me), 2.44 (s, 2H, 4-CH_2), 4.79 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 24.9 (5-Me), 29.0 (N–Me), 29.5 (7-Me), 40.0 (C-4), 53.5 (C-5), 56.4 (C-7), 88.1 (C-3), 115.3 (nitrile), 128.8 (C-3a), 129.8 (C-7a), 160.4 (C-2); MS: *m/z* (%) 249 (1) [M^+], 236 (6), 235 (16), 234 (100), 203 (8), 192 (12), 56 (18); $C_{13}H_{19}N_3S$ (249.36) calcd: C, 62.61, H, 7.68, N, 16.85, S, 12.86. Found: C, 62.44, H, 7.81, N, 16.86, S, 12.84.

Ethyl 2-Amino-5,5,6,7,7-pentamethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylate (**4b**). The same procedure as described for **4a** was performed with **2b** (28.2 g, 100 mmol), Na_2CO_3 (20 g), acetone (300 mL), and MeI (25 mL, 400 mmol). After removal of the solvent at room temperature, the brown residue was treated with H_2O (200 mL), extracted with ether (3 × 150 mL), and dried (Na_2SO_4). Removal of the ether gave a brown oily residue that was refluxed in MeCN (25 mL) for 5 minutes and cooled for 1 hour in an ice bath. The resulting precipitate was collected by filtration and washed with ice-cold MeCN to give **4b**. The brown washings were concentrated in vacuo, cooled in an ice bath, and filtered again to give additional **4b**, totally 7.3 g (25%) of pure **4b** as a colorless solid; mp 116–118°C; ^{1}H NMR

($CDCl_3$): δ 1.13 (s, 6H, 5-Me), 1.34 (s and t, J = 7.1 Hz, 9H, 7-Me and ester Me), 2.37 (s, 3H, N–Me), 2.69 (s, 2H, 4-CH_2), 4.28 (q, 2H, J = 7.1 Hz, O–CH_2), 5.96 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 14.4 (ester Me), 25.0 (5-Me), 29.5 (7-Me), 42.3 (C-4), 53.3 (C-5), 56.2 (C-7), 59.4 (O–CH_2), 105.2 (C-3), 126.9 (C-7a), 129.0 (C-3a), 161.8 (C-2), 166.0 (C=O); $C_{15}H_{24}N_2O_2S$ (296.41) calcd: C, 60.78, H, 8.16, N, 9.45, S, 10.82. Found: C, 60.52, H, 8.10, N, 9.30, S, 10.76.

N′-(3-Cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl)iminoformamide (**5**). Compound **2a** (2.35 g, 10.0 mmol) was refluxed in triethyl orthoformate (15 mL) for 7 hours. The excess triethyl orthoformate was removed in vacuo. The brown solid residue was dissolved in abs. EtOH (60 mL), and the solution was flushed with gaseous NH_3 for 30 minutes while stirring. During the NH_3 treatment, a yellowish-brown solid precipitated. The reaction flask was closed, and the mixture was stirred for another 30 minutes at room temperature. Filtration and washing with abs. EtOH and ether afforded 2.0 g (76%) of crude **5** as a pale yellow solid; mp 205–209°C; ^{1}H NMR (DMSO-d_6): δ 1.10 (s, 6H, 5-Me), 1.30 (s, 6H, 7-Me), 1.89 (br s, 1H, 6-NH), 2.29 (s, 2H, 4-CH_2), 7.53 (broad s, 1H, NH_a), 7.81 (dd, 1H, J = 3.5 and 1.4 Hz, N=CH–N), 7.98 (broad d, 1H, J = 3.5 Hz, NH_b); ^{13}C NMR (DMSO-d_6): δ 29.4 (5-Me), 33.3 (7-Me), 37.0 (C-4), 49.4 (C-5), 51.6 (C-7), 95.4 (C-3), 115.8 (nitrile), 129.6 (C-3a), 131.5 (C-7a), 154.4 (N=CH–N), 165.3 (C-2).

4-Amino-6,6,8,8-tetramethyl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (**6a**). To a solution of NaOEt that was freshly prepared from Na (1.7 g, 74 mmol) and abs. EtOH (80 mL), crude **5** (1.80 g, 6.9 mmol) was added, and the mixture was refluxed for 4 hours. After evaporation of the solvent and addition of brine (100 mL), the mixture was left to stand overnight in a refrigerator. Filtration and recrystallization from MeCN gave 1.35 g (75%) of pure **6a** as light brown crystals; mp 239–240°C; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 6H, 6-Me), 1.49 (s, 6H, 8-Me), 2.75 (s, 2H, 5-CH_2), 5.67 (br s, 2H, NH_2), 8.33 (s, 1H, 2-H); ^{13}C NMR ($CDCl_3$): δ 30.3 (6-Me), 34.1 (8-Me), 39.8 (C-5), 50.0 (C-6), 52.5 (C-8), 115.8 (C-4a), 123.0 (C-4b), 141.8 (C-8a), 152.8 (C-2), 158.0 (C-4), 167.1 (C-9a); $C_{13}H_{18}N_4S$ (262.36) calcd: C, 59.51, H, 6.92, N, 21.36, S, 12.22. Found: C, 59.61, H, 6.99, N, 21.57, S, 12.12.

6,6,8,8-Tetramethyl-3,4,5,6,7,8-hexahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-4-one (**6b**). Compound **2b** (4.23 g, 15.0 mmol) was refluxed in triethyl orthoformate (20 mL) for 6 hours. After removal of the excess orthoester in vacuo, the resulting brown oil was dissolved in abs. EtOH (40 mL) and treated with gaseous NH_3 for 30 minutes. The reaction flask was then closed, the mixture was stirred for 2 hours at room temperature and cooled in a refrigerator for 1 hour. The resulting precipitate was collected by filtration and washed with ice-cooled EtOH to give 1.83 g (46%) of pure **6b** as colorless crystals; mp 235–250°C (slow dec.); ^{1}H NMR (DMSO-d_6): δ 1.05 (s, 6H, 6-Me), 1.38 (s, 6H, 8-Me), 2.78 (s, 2H, 5-CH_2), 8.00 (s, 1H, 2-CH); ^{13}C NMR (DMSO-d_6): δ 29.7 (6-Me), 34.0 (8-Me), 49.3 (C-6), 51.8 (C-8), 122.5 (C-4a), 128.4 (C-4b), 140.4 (C-8a), 144.7 (C-2), 157.9 (C-4), 163.0 (C-9a), C-5 not visible (masked by DMSO signal); $C_{13}H_{17}N_3OS$ (263.35) calcd: C, 59.29, H, 6.51, N, 15.96, S, 12.17. Found: C, 59.19, H, 6.62, N, 15.87, S, 12.11.

4-Amino-6,6,8,8-tetramethyl-2-oxo-1,2,5,6,7,8-hexahydro-pyrido[4′,3′:4,5]thieno[2,3-b]pyridine-3-carbonitrile (**7**). To a solution of NaOEt that was freshly prepared from Na (0.6 g, 26 mmol) and abs. EtOH (25 mL), a solution of ethyl cyanoacetate (1.36 g, 12.0 mmol) in abs. EtOH (15 mL) and **2a** (1.41 g, 6.0 mmol) was added. The mixture was refluxed for 5 hours and left to stand overnight in a refrigerator. The precipitate formed was collected by filtration and washed with EtOH. The ethanolic filtrate was concentrated in vacuo and filtered again. The combined precipitates were dissolved in H_2O (25 mL) to give a brownish clear solution, and the pH was adjusted to 9 by aqueous HCl. The resulting white precipitate was separated by filtration, recrystallized from MeOH/DMSO (1:1), and washed with EtOH to give 0.98 g (54%) of pure **7** as colorless crystals; mp >270°C, ^{1}H NMR (DMSO-d_6): δ 1.15 (s, 6H, 6-Me), 1.38 (s, 6H, 8-Me), 2.75 (s, 2H, 5-CH_2), 6.85 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 29.5 (6-Me), 33.4 (8-Me), 38.3 (C-5), 50.1 (C-6), 51.9 (C-8), 76.6 (C-3), 109.6 (C-4a), 116.9 (nitrile), 125.7 (C-4b), 133.5 (C-8a), 149.8 (C-9a), 156.7 (C-4), 161.0 (C-2); $C_{15}H_{18}N_4OS$ (302.38) calcd: C, 59.58, H, 6.00, N, 18.53, S, 10.60. Found: C, 59.91, H, 6.08, N, 18.68, S, 10.63.

N-(6-Acetyl-3-cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl)acetamide (**8**). A stirred mixture of **2a** (1.41 g, 6.0 mmol) in acetic anhydride (6 mL) was refluxed for 25 minutes. To the resulting black solution, *n*-hexane (5 mL) was added, and the mixture was stirred vigorously for 10 minutes. The resulting precipitate was collected by filtration and washed with ether to give a reddish powder, which was stirred with a solution of HCl (5 drops of 37% HCl in 50 mL of H_2O) for 15 minutes. The

aqueous suspension was filtered affording a reddish solid that was recrystallized from $CHCl_3$/MeCN (3:1) to give 0.65 g (34%) of pure **8** as colorless crystals; mp 246–251°C (dec.); ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 1.37 (s, 6H, 5-Me), 1.69 (s, 6H, 7-Me), 2.176 and 2.182 (2 × s, 6H, 2 × acetyl), 2.64 (s, 2H, 4-CH_2), 11.24 (br s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 22.0 (thiophene *N*-acetyl), 28.4 (6-acetyl), 28.5 (5-Me), 29.5 (7-Me), 39.7 (C-4), 56.8 (C-5), 58.8 (C-7), 91.8 (C-3), 113.7 (nitrile), 127.9 (C-3a), 135.6 (C-7a), 147.2 (C-2), 167.8 (thiophene *N*-acetyl), 172.7 (6-acetyl); MS: *m/z* (%) 319 (79) [M^+], 304 (75), 262 (90), 220 (62), 58 (60), 43 (100); $C_{16}H_{21}N_3O_2S$ (319.41) calcd: C, 60.16; H, 6.63, N, 13.16, S, 10.04. Found: C, 60.07; H, 6.68, N, 13.12, S, 9.99. To the stirred acidic aqueous filtrate, solid Na_2CO_3 was added to adjust to pH 10–11. The white precipitate formed was collected by filtration to give 0.26 g (17%) of pure monoamide **10**; analytical data as given later.

Ethyl N-(3-Cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl)-N-ethoxycarbonylcarbamate (**9**). A stirred mixture of **2a** (0.705 g, 3.0 mmol), dry MeCN (5 mL), and *N*-methylpiperidine (1.09 mL, 9 mmol) was treated dropwise with a solution of ethyl chloroformate (0.58 mL, 6.1 mmol) in dry MeCN (5 mL). The resulting solution was refluxed for 8 hours. Volatile components were removed in vacuo, and the resulting black residue was treated with H_2O (25 mL) and Na_2CO_3 until pH 10. The mixture was extracted with ether (3 × 30 mL), and the combined extracts were washed with brine and H_2O, dried (Na_2SO_4) and concentrated to provide 1.10 g of a reddish-brown oil containing about 85% **9** (NMR). The oil was treated with *n*-hexane (10 mL) at 40–50°C, and the resulting mixture was filtered. The hexane was removed in vacuo. The resulting oil was dissolved in a mixture of H_2O (10 mL) and glacial acetic acid (0.5 mL, 8.7 mmol) and filtered. The clear solution (pH = 4–5) was carefully treated with solid Na_2CO_3 while being stirred vigorously. At pH ~7, the product started to precipitate. At pH = 7.5–8.0, the addition of Na_2CO_3 was stopped and the precipitate collected by filtration and washed with H_2O to give 0.63 g (53%) of pure **9** monohydrate as pale yellow crystals; mp 44–53°C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 6H, 5-Me), 1.26 (t, 6H, J = 7.1 Hz, ethoxy Me), 1.43 (s, 6H, 7-Me), 2.49 (s, 2H, 4-CH_2), 4.27 (q, 4H, J = 7.1 Hz, O–CH_2); ^{13}C NMR ($CDCl_3$): δ 13.9 (ethoxy Me), 29.8 (5-Me), 34.3 (7-Me), 37.8 (C-4), 50.1 (C-5), 52.6 (C-7), 64.3 (O-CH_2), 110.3 (C-3), 112.6 (nitrile), 131.6 (C-3a), 144.6 (C-7a), 145.4 (C-2), 151.3 (C=O); MS: *m/z* (%) 379 (0.4) [M^+ of **9**], 364 (100), 320 (15), 292 (85), 246 (56), 219 (23), 204 (31); $C_{18}H_{25}N_3O_4S$*H_2O (397.47) calcd: C, 54.39, H, 6.85, N, 10.57, S, 8.07. Found: C, 54.63, H, 6.86, N, 10.69, S, 8.04. Heating the hydrate **9***H_2O in vacuo for 20 minutes at 50°C gave pure **9** as a yellowish paste; NMR and MS data as given for **9***H_2O; $C_{18}H_{25}N_3O_4S$ (379.46) calcd: C, 56.97, H, 6.64, N, 11.07, S, 8.45. Found: C, 57.04, H, 6.76, N, 11.24, S, 8.24.

N-(3-Cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl)acetamide (**10**). To a stirred solution of **2a** (2.35 g, 10.0 mmol) in CH_2Cl_2 (30 mL), glacial acetic acid (0.86 mL, 15 mmol) was added dropwise. The mixture was stirred for 30 minutes at room temperature, and the solvent was evaporated. The residue was refluxed in acetic anhydride for 15 minutes. After cooling, ether (30 mL) was added, and the precipitate was separated by filtration and washed with ether. The resulting colorless solid was dissolved in H_2O (100 mL), 2 drops of glacial acetic acid was added, and insoluble impurities were filtered off. To the colorless filtrate, solid Na_2CO_3 was added to adjust to pH 10–11. Filtration and washing with H_2O gave 2.42 g (87%) of pure **10** as a fine white powder; mp 186–188°C; ^{1}NMR ($CDCl_3$): δ 1.20 (s, 6H, 5-Me), 1.45 (s, 6H, 7-Me), 2.28 (s, 3H, N–CO–Me), 2.44 (s, 2H, 4-CH_2), 9.13 (br s, 1H, CO–NH); ^{13}C NMR ($CDCl_3$): δ 23.0 (CO–Me), 29.9 (5-Me), 33.9 (7-Me), 37.6 (C-4), 50.3 (C-5), 52.3 (C-7), 92.4 (C-3), 114.7 (nitrile), 128.2 (C-3a), 135.7 (C-7a), 147.9 (S–C–N), 167.1 (C=O); MS: *m/z* (%) 264 (6), 263 (17), 262 (100) [M^+ − Me], 222 (5), 221 (15), 220 (91), 203 (12), 43 (58), 42 (16); $C_{14}H_{19}N_3OS$ (277.37) calcd: C, 60.62, H, 6.90, N, 15.15, S, 11.56. Found: C, 60.25, H, 6.97, N, 15.16, S, 11.50.

Ethyl N-(3-Cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl)carbamate (**11**). To a solution of **9***H_2O (0.199 g, 0.5 mmol) in EtOH (3 mL), freshly powdered NaOH (0.100 g, 2.5 mmol) was added. The mixture was stirred for 1 hour at 45°C. EtOH was evaporated, and the resulting yellowish solid residue was dissolved in H_2O (15 mL). Insoluble impurities were removed by filtration, and aqueous HCl was added dropwise to the yellow solution to adjust to pH 10–11. The resulting precipitate was collected and washed with H_2O to give 0.133 g (82%) of pure **11** monohydrate as beige crystals; mp 65–74°C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.19 (s, 6H, 5-Me), 1.33 (t, 3H, J = 7.1 Hz, ethoxy Me), 1.43 (s, 6H, 7-Me), 2.43 (s, 2H, 4-CH_2), 4.29 (q, 2H, J = 7.1 Hz, O–CH_2); ^{13}C NMR ($CDCl_3$); δ 14.3 (ethoxy Me), 29.8 (5-Me), 37.6 (C-4), 50.3 (C-5), 52.3 (C-7), 63.0 (O–CH_2), 92.6 (C-3), 114.3 (nitrile), 128.7 (C-3a), 134.9 (C-7a), 148.9 (C-2), 152.5 (C=O); MS: *m/z* (%) = 307 (0.5) [M^+ of **11**], 292 (100), 246 (35), 220 (11),

204 (15); $C_{15}H_{21}N_3O_2S*H_2O$ (325.41) calcd: C, 55.36, H, 7.12, N, 12.91, S, 9.85. Found: C, 55.27, H, 7.24, N, 12.87, S, 10.01. Heating the hydrate **11*** H_2O in vacuo for 1 hour at 100°C gave pure **11** as brownish crystals; mp 151–153°C, NMR and MS data as given for the hydrate **11***H_2O.

Ethyl N-Acetyl-N-(3-cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl)-carbamate (**12**). Ethyl chloroformate (0.10 mL, 1.05 mmol) was added carefully to a stirred solution of **10** (0.277 g, 1.00 mmol) and *N*-methylpiperidine (0.24 mL, 2.0 mmol) in dry MeCN (3 mL), and the mixture was refluxed for 8 hours. Volatile compounds were removed in vacuo. The reddish-brown residue was treated with H_2O (10 mL) and Na_2CO_3 until pH 9 and extracted with ether (2 × 10 mL). The ether extract was dried (Na_2SO_4) and concentrated. The residue thus obtained was heated with *n*-hexane (5 mL) at 40–50°C, and the warm mixture was filtered. The orange-colored filtrate was concentrated to give a red oily residue. This was heated again with *n*-hexane (5 mL) at 40°C, and insoluble impurities were filtered off. The filtrate was concentrated to give 0.20 g (57%) of pure **12** as an orange-colored oil; ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 6H, 5-Me), 1.21 (t, 3H, J = 7.1 Hz, O–CH_2–*Me*), 1.42 (s, 6H, 7-Me), 2.48 (s, 2H, 4-CH_2), 2.61 (s, 3H, CO–Me), 4.22 (q, 2H, J = 7.1 Hz, O–CH_2); ^{13}C NMR ($CDCl_3$): δ 13.9 (OCH_2–*Me*), 26.1 (CO–Me), 29.8 (5-Me), 34.3 (7-Me), 37.8 (C-4), 50.1 (C-5), 52.6 (C-7), 64.1 (O–CH_2), 110.4 (C-3), 112.7 (nitrile), 131.7 (C-3a), 144.9/145.2 (C-2/C-7a), 152.3 (EtO–*C*O–N), 171.8 (Me–*C*O–N); MS: *m/z* (%) 349 (0.4) [M^+], 334 (14), 292 (100), 250 (12), 246 (18), 43 (34), 32 (24); $C_{17}H_{23}N_3O_3S$ (349.43) calcd: C, 58.43, H, 6.63, N, 12.03, S, 9.17. Found: C, 58.74, H, 6.74, N, 12.15, S, 9.10.

Ethyl N-Benzyl-N-(3-cyano-5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl)carbamate (**13**). To a solution of NaOEt, which was freshly prepared from Na (0.024 g, 1.05 mmol) and abs. EtOH (2 mL), **11** (0.307 g, 1.00 mmol) was added, and the mixture was stirred at 50°C. After a few minutes, the mixture became cloudy, indicating the formation of the amide anion. At the same temperature, a solution of BnBr (0.171 g, 1.00 mmol) in abs. EtOH (1 mL) was added dropwise over 15 minutes by means of a syringe while the mixture turned clear again. The mixture was stirred for an additional 12 hours at room temperature, and the solvent was evaporated. The resulting pale yellow residue was treated with H_2O (10 mL) and extracted with ether (2 × 10 mL). After drying (Na_2SO_4) and evaporating the solvent, a yellow oil containing mainly **13** (NMR: about 95% **13**) was obtained. The yellow oil was dissolved in EtOH (5 mL) and cooled to 0°C. To this solution, dilute HBr (5% aqueous solution) was dropped carefully while cooling and observing the pH value. When the solution became strongly acidic (pH ~3), the addition of HBr was stopped, and the solvents were evaporated in vacuo. The residue was triturated with *n*-pentane/ether (3:1), collected by filtration and dissolved in toluene (2 mL). The yellow solution was filtered again, and *n*-hexane was added dropwise under vigorous stirring. The resulting precipitate was separated to give 0.356 g (74%) of pure **13***HBr as fine colorless crystals; mp 97–102°C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, J = 7.1 Hz, ethoxy Me), 1.67 (s, 6H, 5-Me), 1.89 (s, 6H, 7-Me), 2.89 (s, 2H, 4-CH_2), 4.25 (q, 2H, J = 7.1 Hz, O–CH_2), 4.93 (s, 2H, N–CH_2-Ph), 7.15–7.30 (m, 5H, Ph), 9.44 (br s, 2H, H_2N^+). ^{13}C NMR ($CDCl_3$): δ 14.3 (ethoxy Me), 26.6 (5-Me), 31.3 (7-Me), 34.9 (C-4), 54.6 (benzyl CH_2), 58.0 (C-5), 59.1 (C-7), 63.7 (O-CH_2), 107.2 (C-3), 112.6 (nitrile), 127.8, 128.2 (Ph), 128.6 (C-3a), 128.8 (Ph), 134.9 (C-7a), 135.6 (Ph *ipso*-C), 152.8 (C-2), 154.1 (C=O); MS: *m/z* (%) 397 (0.2) [M^+ of **13**], 382 (100), 246 (47), 204 (14), 91 (99), 65 (10), 32 (24); $C_{22}H_{27}N_3O_2S*HBr$ (478.43) calcd: C, 55.23, H, 5.90, N, 8.78, S, 6.70. Found: C, 55.03, H, 6.03, N, 8.66, S, 6.59.

REFERENCES

[1] C. R. Toppin, G. T. Pauly, P. Devanesan, D. Kryak, A. M. Bobst, *Helv. Chim. Acta, 69*(2), 1986, 345.

[2] F. Gugumus, *Polym. Deg. Stab., 40,* 1993, 40 and references cited therein.

[3] C. Navajas, R. Atarah, J. Gynther, *THEOCHEM, 362*(1), 1996, 133.

[4] M. Dagonneau, E. S. Kagan, V. I. Mikhailov, E. G. Rozantsev, V. D. Sholle, *Synthesis,* 1984, 895.

[5] K. Gewald, E. Schinke, H. Böttcher, *Chem. Ber., 99,* 1966, 94.

[6] R. W. Sabnis, *Sulfur Rep., 16*(1), 1994, 1.

[7] (a) A. Rosowsky, M. Chaykowsky, K. K. N. Chen, M. Lin, E. J. Modest, *J. Med. Chem., 16,* 1973, 183. (b) M. Chaykowsky, M. Lin, A. Rosowsky, E. J. Modest, *J. Med. Chem., 16,* 1973, 188. (c) F. J. Tinney, J. P. Sanchez, J. A. Nogas, *J. Med. Chem., 17,* 1974, 624. (d) M. B. Devani, C. J. Shishoo, U. S. Pathak, S. H. Parikh, A. V. Radhakrishnan, A. C. Pandya, *Indian J. Chem., 14B,* 1976, 357. (e) A. S. Noravyan, A. P. Mkrtchyan, R. A. Akopyan, S. A. Vartanyan, *Khim. Farm. Zh., 14,* 1980, 37; *Chem. Abstr. 93,* 1980, 26317.

[8] W. D. Habicher, U. Hähner, S. Schilde, K. Schwetlick: German Patent, DD 283 143 A5 (1990), TU Dresden; *Chem. Abstr. 114,* 1991, 228, 886.

[9] W. D. Habicher, U. Hähner, S. Schilde, K. Schwetlick: German Patent, DD 283 144 A5 (1990), TU Dresden; *Chem. Abstr. 114,* 1991, 207, 251.

[10] K. Gewald, H. Böttcher, R. Mayer, *J. Prakt. Chem., 23,* 1964, 298.
[11] U. Sensfuss, unpublished results.
[12] Simple force field geometry optimizations (MM+), starting from a chair conformation, resulted only in a small difference between triacetonamine (**1**) and *N*-methyltriacetonamine: The average distance from C-3 to the 2-methyl carbons was 2.23 A° for *N*-methyltriacetonamine with an equatorial *N*-methyl group, whereas the same calculations with **1** gave average distances of 2.24 A° for an equatorial *N*-hydrogen and 2.25 A° for an axial *N*-hydrogen.
[13] E. C. Taylor, J. G. Berger, *J. Org. Chem., 32,* 1967, 2376.
[14] K. Gewald, E. Martin, *J. Prakt. Chem., 323,* 1981, 843.
[15] K. Gewald, H. Schäfer, K. Sattler, *Monatsh. Chem., 110,* 1979, 1189.
[16] K. Gewald, G. Neumann, *Chem. Ber., 101,* 1968, 1933.
[17] R. A. Crochet, J. T. Boatright, C. DeWitt Blanton, C. T. Wie, W. E. Hochholzer, *J. Heterocycl. Chem., 11,* 1974, 143.