# SYNTHESIS, DEHYDRATION AND OXIDATION OF 3-CYANO-4,6-DIARYL-5-ETHOXYCARBONYL-6-HYDROXYPIPERIDINE-2-THIONES

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**Abstract:** 6-Hydroxypiperidine-2-thiones **2** and 1,4-dihydropyridine-2(3H)-thiones **3** were obtained by an unsymmetrical condensation of ethyl 4-nitrobenzoylacetate, an aromatic aldehyde and cyanothioacetamide in the presence of piperidine with subsequent acidification. Oxidation of piperidine-2-thiones **2** with iodine yielded 2,2'-bis(1,4,5,6-tetrahydropyridyl)disulfides **4**. 2,2'-Bis(1,4-dihydropyridyl)disulfides **5** were obtained by treatment of **1** or **4** with hydrochloric acid, or by oxidation of 1,4-dihydropyridine-2(3H)-thiones **3** with iodine.

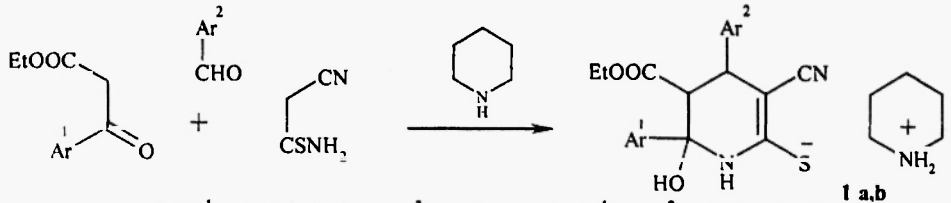
## Introduction

3-Cyano-1,4-dihydropyridine-2(3H)-thiones are of interest due to their high reactivity [1] and revealed cardiovascular [2,3], antioxidant and hepatoprotective [4,5] activities. 3-Cyano-6-hydroxy-1,4,5,6-tetrahydropyridine-2-thiones as betaines have been obtained only in the case of bearing pyridinio type cation in 5 position [6,7]. 2-Alkylthio-6-hydroxy-1,4,5,6-tetrahydropyridines without strong electron withdrawing group at 5 position and sterically bulky group at 6 position were unstable compounds while they in course of preparation split off water molecule to give 2-alkylthio-1,4-dihydropyridines [8-10].

We have firstly isolated stable 3-cyano-6-hydroxypiperidine-2-thiones bearing electron withdrawing ethoxycarbonyl and 4-nitrophenyl groups at respectively 5 and 6 positions and obtained corresponding 2,2'-bis(1,4,5,6-tetrahydropyridyl)disulfides.

## Results and discussion

Piperidinium 6-hydroxy-1,4,5,6-tetrahydropyridine-2-thiolates **1** as starting materials were obtained in 83 – 89 % yield by unsymmetrical condensation of ethyl 4-nitrobenzoylacetate, an aromatic aldehyde and cyanothioacetamide in the presence of piperidine (Scheme 1).



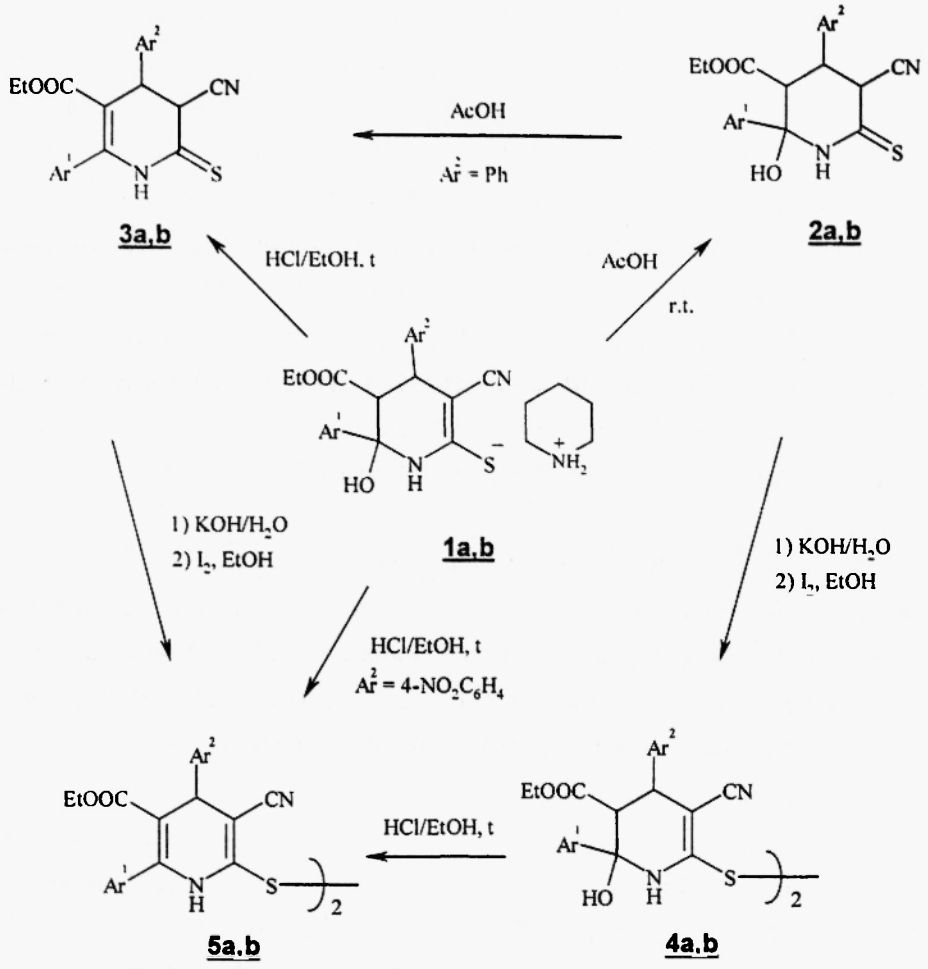

a) $Ar^1 = 4\text{-}NO_2C_6H_4$, $Ar^2 = C_6H_5$; b) $Ar^1 = Ar^2 = 4\text{-}NO_2C_6H_4$

**Scheme 1**

By the treatment of thiolates 1 at room temperature with acetic acid 6-hydroxypiperidine-2-thiones 2 in 93 – 94 % yield were obtained. 1,4-Dihydropyridine-2(3H)-thione 3a (80 %) was obtained on short heating of thiolate 1a with hydrochloric acid in ethanol, but thione **3b** (89 %) was formed on 30 min reflux in acetic acid. In the case of heating of 1b with HCl/EtOH a mixture of 2,2'-bis(1,4-dihydropyridyl)disulfide 5b (55 %) and thione 3b (18 %) was formed, which was separated by fractional crystallization. By the treatment of thiones 2 at room temperature with equimolar amount of iodine-ethanol solution 2,2'-bis(1,4,5,6-tetrahydropyridyl)disulfides 4 were isolated in 63 –72 % yield. 2,2'-Bis(1,4-dihydropyridyl)disulfides 5 were prepared in 90 – 96 % yield by short heating of 4 with hydrochloric acid in ethanol. Oxidation of thione 3b with iodine-ethanol solution led to formation of mixture from which only 35 % of 5b was isolated (Scheme 2).

The structure of synthesized compounds was proved by spectroscopic methods. In the IR spectra absorbtion bands of νC≡N for thiolates 1 at 2166 – 2168 $cm^{-1}$, for disulfides 4, 5 at 2196 – 2200 $cm^{-1}$, but for 3-cyanopiperidine-2-thiones 2 and 3-cyano-1,4-dihydropyridine-2(3H)-thiones 3 at 2266 – 2268 and 2254 $cm^{-1}$, correspondingly, are observed. Absorbtion bands of νC=O of compounds are in agreement with the type of conjugation of C=O groups. The doublets in the case of $^1H$ NMR spectra of 1 and 4, with $J_{4,5}$ = 12 Hz according to [11] confirm a trans-diaxial configuration of the 4-H and 5-H protons. In the $^1H$ NMR spectra of 2 the characteristic three adjacent proton system with $J_{3,4}$ = 11,2 – 11,8 Hz and $J_{4,5}$ = 12,2 – 12,4 Hz occurs, confirming the trans-arrangement of substituents in position 3 and 5 referring to 4-aryl group. The $^1H$ NMR spectra of 3 revealed that they are formed as a mixture of cis- and trans-stereoisomers (ratio ~ 3:2). In case of 1,4-dihydropyridines 5 the characteristic 4-H proton signals at 4.77 and 4.87 ppm are observed. The structure of piperidine-2-thione 2a is confirmed by $^{13}C$ NMR spectrum.

In conclusion a convenient method of the synthesis of 3-cyano-6-hydroxypiperidine-2-thiones 2 has been elaborated. Up to now 6-hydroxypiperidine-2-thiones 2 and 2,2'-bis-(6-hydroxy-1,4,5,6-tetrahydropyridyl)disulfides 4 were not described in literature. The introduction of electron withdrawing 4-nitrophenyl group at 6 position enhances the stability and diminishes solubility which allow to isolate 2 and 4 in high yields.




**a) $Ar^1 = 4\text{-}NO_2C_6H_4$, $Ar^2 = C_6H_5$; b) $Ar^1 = Ar^2 = 4\text{-}NO_2C_6H_4$**

**Scheme 2**

## Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 580 B spectrometer (in nujol) and peak positions $\nu_{max}$ were expressed in $cm^{-1}$. $^1H$ NMR spectra were recorded on a Bruker WH-90 (90 MHz) and AM-360 (360 MHz) spectrometers. Chemical shifts are expressed in δ (p.p.m. downfield from TMS) and coupling constants (*J*) in Hz. The course of the reactions and the individuality of substances were monitored by TLC on Kieselgel 60 F Merck plates with dichloromethane – hexane – methanol (5 : 5 : 1) as eluent. Compounds were recrystallized from ethanol.

**Piperidinium 3-cyano-4,6-diaryl-5-ethoxycarbonyl-6-hydroxy-1,4,5,6-tetrahydropyridine-2-thiolates 1.**

A mixture of ethyl 4-nitrobenzoylacetate (4.75 g, 20 mmol), benzaldehyde (2.12 g, 20 mmol) and cyanothioacetamide (2.0 g, 20 mmol) in 40 ml of ethanol and piperidine (2 ml, 20 mmol) was shortly heated untill dissolution and stirred for 30 min at ambient temperature. The precipitate was filtered and washed with

30 ml of cooled ethanol to give 9.1 g (89 %) of **1a** as slightly yellow powder, mp >110°C (decomp.); IR (ν/cm): 1730 (C=O); 2168 (C≡N); 3242, 3426 (NH, OH); $^1$H NMR ($CDCl_3$, δ, ppm): 0.52 (3H, t, $CH_2\underline{CH_3}$); 1.55 [6H, m, $(CH_2)_3$]; 2.80 [4H, m, $N(CH_2)_2$]; 2.98 (1H, d, J = 12 Hz, 5-H); 3.52 (2H, q, $\underline{CH_2}CH_3$); 4.08 (1H, d, J = 12 Hz, 4-H); 5.86 (1H, s, OH); 7.1 – 7.3 (5H, m, 4-$C_6H_5$); 7.78 and 8.14 (4H, d and d, 6-$C_6H_4$). Anal. Calcd.for $C_{26}H_{30}N_4O_5S$: C 61.16, H 5.92, N 10.97, S 6.28. Found C 61.20, H 6.00, N 10.93, S 6.30.

In a similar manner (4-nitrobenzaldehyde was used instead of benzaldehyde) thiolate **1b** (yield 83 %) was obtained as slightly yellow powder ; mp >110°C (decomp.); IR (ν/cm): 1721 (C=O); 2166 (C≡N); 3332, 3400 (NH, OH); $^1$H NMR ($CDCl_3$, δ, ppm): 0.55 (3H, t, $CH_2\underline{CH_3}$); 1.67 [6H, m, $(CH_2)_3$]; 2.98 (1H, d, J = 12 Hz, 5-H); 3.05 [4H, m, $N(CH_2)_2$]; 3.56 (2H, q, $\underline{CH_2}CH_3$); 4.30 (1H, d, J = 12 Hz, 4-H); 5.90 (1H, s, OH); ~ 6.1 (3H, complex, NH and $+NH_2$); 7.50 and 8.12, 7.78 and 8.22 (8H, d and d, d and d, 4,6-$C_6H_4$). Anal. Calcd.for $C_{26}H_{29}N_5O_7S$: C 56.22, H 5.26, N 12.61, S 5.77. Found C 56.37, H 5.20, N 12.51, S 5.90.

**3-Cyano-4,6-diaryl-5-ethoxycarbonyl-6-hydroxypiperidine-2-thiones 2.**

Thiolate **1a** (1.02 g, 2 mmol) in 5 ml of ethanol was treated with 5 ml of acetic acid under stirring at room temperature for one hour. The precipitate was filtered, washed with 20 ml of water and 5 ml of ethanol to give 0.8 g (94 %) **2a** as colourless powder, mp 131 – 134°C; IR (ν/cm): 1728 (C=O); 2268 (C≡N); 3296 (NH, OH). $^1$H NMR (DMSO-$d_6$, δ, ppm): 0.54 (3H, t, $CH_2\underline{CH_3}$); 3.50 (2H, q, $\underline{CH_2}CH_3$); 3.75 (1H, d, J = 12,4 Hz, 5-H); 4.01 (1H, dd, J = 11.2 and 12,4 Hz, 4-H); 4.88 (1H, d, J = 11.2 Hz, 3-H); 7.2 – 7.4 (5H, m, 4-$C_6H_5$); 7.65 (1H, s, OH); 7.82 and 8.26 (4H, d and d, 6-$C_6H_4$); 11.38 (1H, s, NH). $^{13}$C NMR (DMSO-$d_6$,): 13.34 ($CH_3$); 40.77 (4-C); 49.64 (3-C); 55.46 (5-C); 59.78 ($CH_2$); 83.90 (6-C); 117.53 (CN); 122.90, 128.52, 127.79, 127.95, 128.23, 138.91, 147.28, 148.94 ($C_6H_4NO_2$ and $C_6H_5$); 166.93 (C=O); 192.50 (C=S). Anal.Calcd. for $C_{21}H_{19}N_3O_5S$: C 59.28, H 4.50, N 9.88, S 7.54. Found: C 59.57, H 4.47, N 9.83, S 7.55.

In a similar manner thione **2b** (yield 93 %) was obtained as slightly yellow powder ; mp 128 - 130°C; IR (ν/cm): 1717 (C=O); 2266 (C≡N); 3298, 3624 (NH, OH). $^1$H NMR (DMSO-$d_6$, δ, ppm): 0.56 (3H, t, $CH_2\underline{CH_3}$); 3,56 (2H, q, $\underline{CH_2}CH_3$); 3.88 (1H, d, J = 12.2 Hz, 5-H); 4.24 (1H, dd, J = 11.8 and 12,4 Hz, 4-H); 5.00 (1H, d, J = 11.8 Hz, 3-H); 7.62 (1H, s, OH); 7.73 and 8.27, 7.82 and 8.31 (8H, d and d, d and d, 4,6-$C_6H_4$); 11.50 (1H, s, NH). Anal.Calcd. for $C_{21}H_{18}N_4O_7S$: C 53.61, H 3.86, N 11.91, S 6.81. Found: C 53.52, H 3.88, N 11.81, S 6.90.

**3-Cyano-4,6-diaryl-5-ethoxycarbonyl-1,4-dihydropyridine-2(3H)-thiones 3.**

Thiolate **1a** (1.02 g, 2 mmol) in 10 ml of ethanol and 5 ml of conc. hydrochloric acid was refluxed for 5 min, cooled to room temperature and 5 ml of water was added. The precipitate was filtered, washed with 10 ml of ethanol and 10 ml of water to give 0.65 g (80 %) **3a** as yellow powder, mp >100°C (decomp.); IR (ν/cm): 1672, 1707 (C=O); 2254 (C≡N); 3220 (NH). $^1$H NMR (DMSO-$d_6$, δ, ppm): 0.90 and 0.92 (3H, t and t, cis-

and trans- $CH_2\underline{CH_3}$); 3,90 and 3.92 (2H, q and q, cis- and trans-$\underline{CH_2}CH_3$); 4.28 [0.4 H, d, J = 2,6 Hz, trans-(3-H)]; 4.43 [0.6H, d, J = 6.6 Hz, cis-(3-H)]; 4.54 [0.6H, d, J = 6.6 Hz, cis-(4-H)]; 4.60 [0.4H, d, J = 2.6 Hz, trans-(4-H)]; 7.2 - 8.4 [9H, complex, cis- and trans- (4-$C_6H_5$ and 6-$C_6H_4$)]; 8.75 (1H, broad s, cis- and trans-NH). Anal.Calcd. for $C_{21}H_{17}N_3O_4S$: C 61.91, H 4.21, N 10.31, S 7.87. Found: C 61.65, H 4.14, N 10.12, S 7.71.

Thione **2b** (1.41 g, 3 mmol) in 15 ml of acetic acid was refluxed for 30 min and cooled to room temperature. The precipitate was filtered and washed with 5 ml of ethanol to give 1.20 g (89 %) of **3b** as yellow powder, mp >120°C; IR (ν/cm): 1696, 1716 (C=O); 2254 (C≡N); 3182 (NH). $^1$H NMR ($CDCl_3$, δ, ppm): 0.88 and 0.90 (3H, t and t, cis- and trans- $CH_2\underline{CH_3}$); 3,90 and 3.92 (2H, q and q, cis- and trans-$\underline{CH_2}CH_3$); 4.30 [0.4 H, d, J = 2.8 Hz, trans-(3-H)]; 4.50 [0.6H, d, J = 6.6 Hz, cis-(3-H)]; 4.66 [0.6H, d, J = 6.6 Hz, cis-(4-H)]; 4.72 [0.4H, d, J = 2.6 Hz, trans-(4-H)]; 7.4 - 8.4 [8H, complex, cis- and trans-(4,6-$C_6H_4$)]; 9.06 (0.6H, broad s, cis-NH); 9.10 (0.4H, br.s, trans-NH). Anal.Calcd. for $C_{21}H_{16}N_4O_6S$: C 55.75, H 3.56, N 12.38, S 7.09. Found: C 55.49, H 3.72, N 12.29, S 6.95.

**2,2'-Bis-(3-cyano-4,6-diaryl-5-ethoxycarbonyl)-6-hydroxy-1,4,5,6-tetrahydropyridyl)disulfides 4.**

To a mixture of thione **2a** (4.25 g, 10 mmol) and 3 ml of 3 M KOH in 50 ml of ethanol during 30 min 20 ml of 0.5 M iodine-ethanol solution was added and stirred for 1 h at room temperature. The precipitate was filtered, washed with 50 ml of ethanol, 10 ml of water and 10 ml of ethanol to give 2.66 g (63 %) of **4a** as colourless powder, mp >170°C (decomp.); IR (ν/cm): 1738 (C=O); 2196 (C=N); 3320, 3388 (NH, OH); $^1$H NMR (DMSO-$d_6$, δ, ppm): 0.52 (3H, t, $CH_2\underline{CH_3}$); 3.02 (1H, d, J = 12 Hz, 5-H); 3.48 (2H, q, $\underline{CH_2}CH_3$); 4.26 (1H, d, J = 12 Hz, 4-H); 6.86 (1H, s, OH); 7.1 – 7.3 (5H, m, 4-$C_6H_5$); 7.90 and 8.32 (4H, d and d, 6-$C_6H_4$); 8.62 (1H, s, NH). Anal. Calcd.for $C_{42}H_{36}N_6O_{10}S_2$ : C 59.42, H 4.27, N 9.90, S 7.55. Found C 59.29, H 4.15, N 9.83 , S 7.54.

In a similar manner disulfide **4b** (yield 72 %) was obtained as slightly yellow powder ; mp >180°C (decomp.). IR (ν/cm): 1740 (C=O); 2200 (C=N); 3322, 3400 (NH, OH); $^1$H NMR (DMSO-$d_6$ , δ, ppm): 0.48 (3H, t, $CH_2\underline{CH_3}$); 3.02 (1H, d, J = 12 Hz, 5-H); 3.50 (2H, q, $\underline{CH_2}CH_3$); 4.44 (1H, d, J = 12 Hz, 4-H); 6.98 (1H, s, OH); 7.67 and 8.12, (4H, d and d, 4-$C_6H_4$); 7.88 and 8.27 (4H, d and d, 6-$C_6H_4$); 8.78 (1H, s, NH). Anal. Calcd.for $C_{42}H_{34}N_8O_{14}S_2$ : C 53.73, H 3.65, N 11.93, S 6.83. Found C 53.48, H 3.48, N 11.74, S 6.90.

**2,2'-Bis-(3-cyano-4,6-diaryl-5-ethoxycarbonyl)-6-hydroxy-1,4-dihydropyridyl)-disulfides 5a.** Disulfide **4a** (0.85 g, 1 mmol) in 60 ml of 0.5 M hydrochloric acid solution in ethanol was refluxed for 15 min, cooled and stirred at ambient temperature for 1 hour. The precipitate was filtered, washed with 20 ml of ethanol to give 0.73 g (90 %) **5a** as slightly yellow powder, mp 203 – 205°C; IR (ν/cm): 1653 (C=O); 2198 (C≡N); 3200, 3228 (NH). $^1$H NMR (DMSO-$d_6$, δ, ppm): 0.72 (3H, t, $CH_2\underline{CH_3}$); 3,68 (2H, q, $\underline{CH_2}CH_3$); 4.77 (1H, s,

4-H); 7.40 (5H, m, 4-$C_6H_5$); 7.72 and 8.26 (4H, d and d, 6-$C_6H_4$); 10.36 (1H, broad s, NH). Anal. Calcd.for $C_{42}H_{32}N_6O_8S_2$ : C 62.06, H 3.97, N 10.34, S 7.89. Found C 61.89, H 3.94, N 10.26, S 7.83.

In a similar manner disulfide **5b** (yield 96 %) was obtained as slightly yellow powder ; mp 190 - 192°C (decomp.). IR (ν/cm): 1686, 1700 (C=O); 2198 (C≡N); 3260 (NH); $^1$H NMR (DMSO-$d_6$ , δ, ppm): 0.68 (3H, t, $CH_2\underline{CH_3}$); 3.66 (2H, q, $\underline{CH_2}CH_3$); 4.87 (1H, s, 4-H); 7.62 and 8.20, 7.70 and 8.28 (8H, d and d, d and d, 4,6-$C_6H_4$); 10.42 (1H, s, NH). Anal. Calcd.for $C_{42}H_{30}N_8O_{12}S_2$ : C 55.87, H 3.35, N 12.41, S 7.10. Found C 55.78, H 3.40, N 12.24, S 7.11.

**Treatment of 1b with hydrochloric acid.**

Thiolate **1b** (2.79 g, 5 mmol) in 25 ml of ethanol and 4 ml of conc. hydrochloric acid was refluxed for 10 min and cooled to room temperature. The precipitate was filtered, washed with 5 ml of ethanol and 5 ml of water to give 1.12 g (62 %) of **5b**. To the filtrate stepwise 10 ml of water was added. The precipitate was filtered, washed with 20 ml of water, 5 ml of ethanol to give 0.41 g (18 %) of **3b**.

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