SYNTHESIS AND PROPERTIES OF METHYL 4,6-DIARYL-2(3H)-THIOXO-1,4-DIHYDROPYRIDINE-3-CARBOXYLATES

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Abstract: Methyl 4,6-diaryl-2(3H)-thioxo-1,4-dihydropyridine-3-carboxylates (**5**) were obtained by Michael reaction of arylmethylideneacetophenones **1** with methyl 2-thiocarbamoylacetate (**2**) in the presence of piperidine with subsequent treatment with HCl / EtOH solution. Methyl 2-carbamoylmethylthio-1,4-dihydropyridine-3-carboxylates **7** were prepared by alkylation of thiones **5** with iodoacetamide, but methyl 3-ethoxycarbonylmethyl-4,7-dihydrothiazolo[3,2-a]pyridine-8-carboxylate **8** - by treatment of thione **5a** with ethyl 4-chloroacetoacetate in the presence of equimolar amount of triethylamine.

Introduction

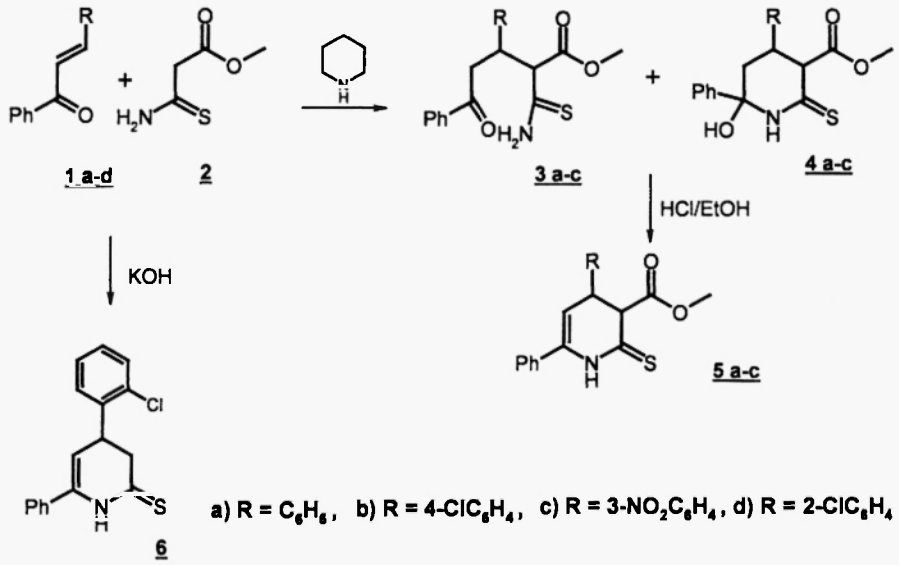
2(3H)-Thioxo-1,4-dihydropyridine-3-carbonitriles are of interest due to their high reactivity [1] and revealed cardiovascular [2,3], hepatoprotective [4], antioxidant [5] and antiradical [6] activities. A shortcoming of 2(3H)-thioxo-1,4-dihydropyridine-3-carbonitriles is their instability in diluted solutions and insufficient solubility for detailed biological investigation. Introduction of 3-COOMe group instead of 3-CN group in the 1,4-dihydropyridine-2(3H)-thione skeleton could increase the solubility and the lipophilicity of them.

Results and discussion

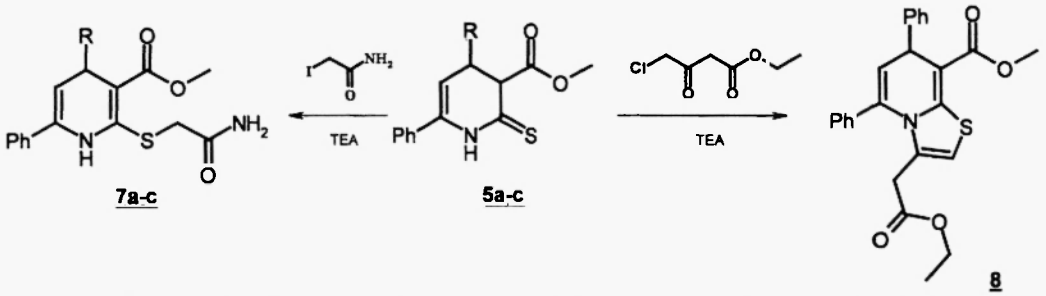
Methyl 2(3H)-thioxo-1,4-dihydropyridine-3-carboxylates **5** were obtained by Michael reaction of arylmethylideneacetophenones **1** with methyl 2-thiocarbamoylacetate (**2**) in the presence of stoichiometric amount of piperidine as a promotor with subsequent treatment of formed mixture with HCl / EtOH solution.

Stirring of compounds **1**, **2** and piperidine in ethanol at room temperature gave rise to the mixture of primary Michael adducts: methyl 3-benzoyl-1-thiocarbamoylbutyrates **3** and the

products of further heterocyclization – methyl 6-hydroxy-2-thioxopiperidine-3-carboxylates **4**. The **3** to **4** ratio according to ^{1}H NMR data was approximately 1:1. Application of stronger bases: sodium methylate or potassium hydroxide and elevation of reaction temperature in the case of condensation of chalcones **1** with 2-cyanothioacetamide yielded 2(3H)-thioxo-1,4-dihydropyridine-3-carbonitriles and the corresponding 2(1H)-thioxopyridine-3-carbonitriles [7,8], but by making use of methyl 2-thiocarbamoylacetate (**2**) as Michael donor gave rise to further hydrolysis and decarboxylation of ester group of thiones **5** and complicated reaction mixture was formed usually. Only in the case of condensation of 2-chlorophenylmethyleneacetophenone (**1d**) with **2** in the presence of KOH 3,4-dihydropyridine-2(1H)-thione **6** was isolated (yield 22 %) as the main product. Thione **6** with 45 % yield was obtained in case of making use piperidine.



Alkylation of thiones **5** with iodoacetamide in the presence of stoichiometric amount of triethylamine leads to formation of methyl 2-carbamoylmethylthio-1,4-dihydropyridine-3-carboxylates **7**, but treatment of thione **5a** with ethyl 4-chloroacetoacetate yielded methyl 3-ethoxycarbonylmethyl-4,7-dihydrothiazolo[3,2-a]pyridine-8-carboxylate **8**. We did not succeed to isolate ethyl 2-methoxycarbonylmethylcarbonylmethylthio-1,4-dihydropyridine-3-carboxylate **9**, which in the course of reaction underwent further heterocyclization involving acetyl group and nitrogen atom of dihydropyridine ring to close thiazolo[3,2-a]pyridine ring **8**. Similar cascade reaction was observed in the case of formation of 8-ethoxycarbonylmethyl substituted hydrogenated thiazolo[2,3-c][1,4]thiazines [9].



The structure of synthesized compounds was proved by spectroscopic methods. In the IR spectra characteristic absorption bands of $\nu_{C=O}$ of ester group in position 3 (bounded with unsaturated carbon atom) for thiones **3-5** at 1730-1753 cm^{-1}, but for compounds **7**, **8** (being in conjugation) at 1663-1696 cm^{-1} were observed.

In the ^1H NMR spectra of thiones **5** characteristic signals of 3-H, 4-H and 5-H were observed at 4.02-4.08 (d), 4.22-4.39 (dd) and 5.71-5.76 (dd) ppm, subsequently. In case of 5-H protons long-range coupling with NH (J =1.6 Hz) are observed. Contrary to the mixture of cis- and trans-3-cyano-1,4-dihydropyridine-2(3H)-thiones [10], thiones **5** with sterically more bulky COOMe group in position 3 were formed as single isomers. $^3J_{3,4}$ = 8.4-8.5 Hz more corresponds to trans-diaxial configuration of the 4-H and 5-H protons [11]. The structures of compounds **7**, **8** were confirmed by doublets from 4-H and 5-H with J = 6.4-7.0 Hz.

So, methyl 4,6-diaryl-2(3H)-thioxo-1,4-dihydropyridine-3-carboxylates (**5**) were obtained and characterized. 2-Carbamoylmethylthio-3-methoxycarbonyl-1,4-dihydropyridines **7** and methyl 3-ethoxycarbonylmethyl-4,7-dihydrothiazolo[3,2-a]pyridine-8-carboxylate **8** were obtained by alkylation of thiones **5**.

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 ν_{max} were expressed in cm^{-1}. ^1H NMR spectra were recorded on a Bruker WH-90 (90 MHz) apparatus and chemical shifts are expressed in δ (ppm 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.

Reaction of arylmethylideneacetophenones with methyl 2-thiocarbamoylacetate.

A mixture of chalcone (**1a**) (2.08 g, 10 mmol), methyl 2-thiocarbamoylacetate (**2**) (1.33 g, 10 mmol) and piperidine (1 ml, 10 mmol) in 10 ml of methanol was stirred at room temperature for 1h. Then reaction mixture was cooled to –10°C, the precipitate was separated by filtration and washed with 10 ml of cold

methanol to give 2.36 g (69 %) of a mixture of **methyl 3-benzoyl-2-phenyl-1-thiocarbamoylbutyrate** (**3a**) and **methyl 4,6-diphenyl-6-hydroxy-2-thioxo-piperidine-3-carboxylate** (**4a**). IR (ν/cm): 1680, 1730 (C=O); 3274, 3386 (NH, OH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.18 – 4.28 [8H, complex, 2(CH-CH-CH_2)]; 3.38 and 3.44 (6H, s and s, 2OMe) 6.80 (1H, s, OH); 7.0 – 7.8 (20H, m, 4Ph); 9.60 and 9.86 (2H, s and s, NH_2); 10.60 (1H, s, NH). Anal. Calcd.for $C_{19}H_{19}NO_3S$: C 66.84, H 6.61, N 4.10, S 9.39. Found: C 66.83, H 5.58, N 4.18, S 9.38.

In a similar manner [4-chlorophenylmethyleneacetophenone (**1b**) was used instead of chalchone (**1a**)] a mixture of **3b** and **4b** with 56 % yield was obtained. IR (ν/cm): 1651, 1677, 1732 (C=O); 3180, 3314, 3365 (NH, OH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.24 – 4.30 [8H, complex, 2(CH-CH-CH_2)]; 3.60 (6H, s, 2OMe); 6.80 (1H, s, OH); 7.1 – 7.9 (18H, m, $2C_6H_5$ and $2C_6H_4$); 9.27 and 9.31 (2H, br.s and br.s, NH_2); 10.62 (1H, s, NH). Anal. Calcd.for $C_{19}H_{18}ClNO_3S$: C 60.71, H 4.83, N 3.73, S 8.53. Found: C 60.76, H 4.72, N 3.56, S 8.55.

In a similar manner [3-nitrophenylmethyleneacetophenone (**1c**) was used instead of chalchone (**1a**)] a mixture of **3c** and **4c** with 75 % yield was obtained. IR (ν/cm): 1640, 1695, 1753 (C=O); 3130, 32944, 3378 (NH, OH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.12 – 4.40 [8H, complex, 2(CH-CH-CH_2)]; 3.40 and 3.46 (6H, s and s, 2OMe); 6.90 (1H, s, OH); 7.3 – 8.3 (18H, m, $2C_6H_5$ and $2C_6H_4$); 9.70 and 9.94 (2H, br.s and br.s, NH_2); 10.68 (1H, s, NH). Anal. Calcd.for $C_{19}H_{18}N_2O_5S$: C 59.08, H 4.70, N 7.25, S 8.30. Found: C 59.20, H 4.54, N 7.30, S 8.63.

Methyl 4,6-diaryl-2(3H)-thioxo-1,4-dihydropyridine-3-carboxylate (**5a**).

A mixture of compounds **3a** and **4a** (1.71 g, 5 mmol) was refluxed in 12 ml of 1M HCl/EtOH solution for 15 min and stirred at the ambient temperature for 45 min. Then reaction mixture was cooled to –10°C, the precipitate was filtered and washed with 10 ml of cold ethanol to give 1.35 g (83 %) of **5a** as yellow crystals. M.p. 142 – 143°C (from ethanol). IR (ν/cm): 1735 (C=O); 3282 (NH); ^{1}H NMR ($CDCl_3$, δ, ppm): 3.70 (3H, s OMe); 4.07 (1H, d, J = 8.4 Hz, 3-H); 4.24 (1H, dd, J = 4.6 and 8.5 Hz, 4-H); 5.76 (1H, dd, J = 1.6 and 4.6 Hz, 5-H); 7.2 – 7.5 (10H, complex, 4,6-C_6H_5); 9.11 (1H, s, NH). Anal. Calcd.for $C_{19}H_{17}NO_2S$: C 70.56, H 5.30, N 4.33, S 9.91. Found: C 70.31, H 5.39, N 4.35, S 9.86.

In a similar manner from a mixture of **3b** and **4b** thione **5b** with 70 % yield as yellow crystals was obtained. M.p. 159 – 161°C (from ethanol). IR (ν/cm): 1742 (C=O); 3186 (NH); ^{1}H NMR ($CDCl_3$, δ, ppm): 3.70 (3H, s OMe); 4.02 (1H, d, J = 8.5 Hz, 3-H); 4.22 (1H, dd, J = 4.6 and 8.5 Hz, 4-H); 5.71 (1H, dd, J = 1.5 and 4.5 Hz, 5-H); 7.21 and 7.29, and 7.4 - 7.5 (9H, d and d, m, 4-C_6H_4, 6-C_6H_5); 9.13 (1H, s, NH). Anal. Calcd.for $C_{19}H_{16}ClNO_2S$: C 63.77, H 4.51, N 3.91, S 8.96. Found: C 63.93, H 4.11, N 3.83, S 9.72.

In a similar manner from a mixture of **3c** and **4c** thione **5c** with 75 % yield as yellow crystals was obtained. M.p. 165 – 167 °C (from ethanol). IR (ν/cm): 1742 (C=O); 3186 (NH); ^{1}H NMR ($CDCl_3$, δ, ppm): 3.72 (3H, s OMe); 4.08 (1H, d, J = 8.4 Hz, 3-H); 4.39 (1H, dd, J = 4.6 and 8.5 Hz, 4-H); 5.74 (1H, dd, J = 1.6

and 4.6 Hz, 5-H); 7.4 – 8.4 (10H, complex, 4-C_6H_4, 6-C_6H_5); 9.15 (1H, s, NH). Anal. Calcd.for $C_{19}H_{16}N_2O_4S$: C 61.94, H 4.38, N 7.60, S 8.70. Found: C 62.06, H 4.18, N 7.41, S 8.50.

4-(2-Chlorophenyl)-6-phenyl-3,4-dihydropyridine-2(1H)-thione (6).

A mixture of 2-chlorophenylmethyleneacetophenone (**1d**) (2.42 g, 10 mmol), methyl 2-thiocarbamoylacetate (**2**) (1.33 g, 10 mmol) and 1 ml (10 mmol) of piperidine (or 5 ml 2M KOH solution in water) in 10 ml of methanol was stirred at room temperature for 6h. Then gradually 5 ml of water was added and reaction mixture was cooled to 0°C. The precipitate was filtered and washed with 10 ml of cold methanol to give 1.35 g or 0.65 g (45 % and 22 %, subsequently) of **6** as grey crystals. M.p. 174 – 176 °C (from ethanol). IR (ν/cm): 3174 (NH). ^{1}H NMR ($CDCl_3$, δ, ppm): 3.26 (2H, ddd, J = 7.4, 8.5 and 17.0 Hz, 3-H_2); 4.34 (1H, m, 4-H); 5.82 (1H, dd, J = 1.6 and 4.6 Hz, 5-H); 7.2-7.5 (9H, complex, 4-C_6H_4, 6-C_6H_5); 9.09 (1H, s, NH). Anal. Calcd.for $C_{17}H_{14}ClNS$: C 68.10, H 4.71, N 4.61, S 10.69. Found: C 67.95, H 4.60, N 4.45, S 10.70.

Methyl 2-carbamoylmethylthio-4,6-diphenyl-1,4-dihydropyridine-3-carboxylate (7a).

A mixture of thione **5a** (0,65 g, 2 mmol), iodoacetamide (0,37 g, 2 mmol) and triethylamine (0.28 ml, 2 mmol) in 20 ml of ethanol was shortly heated till dissolution and stirred at ambient temperature for two hours. The precipitate was filtered and washed with 10 ml of cold ethanol, 20 ml of water and 5 ml of cold ethanol to give 0.43 g (62 %) of **7a** as slightly yellow powder. M.p. 180 – 182 °C (from ethanol). IR (ν/cm): 1666, 1696 (C=O); 3195, 3368 (NH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.42 (3H, s OMe); 3.53 and 3.75 (2H, d and d, J = 14 Hz, SCH_2); 4.62 and 5.36 (2H, d and d, J = 6.4 Hz, 4-H and 5-H); 7.0 – 7.5 (10H, complex, 4,6-Ph); 7.58 and 8.00 (2H, br.s and br. s, $CONH_2$); 10.02 (1H, s, NH). Anal. Calcd.for $C_{21}H_{20}N_2O_4S$: C 66.30, H 5.30, N 7.36, S 8.43. Found: C 65.95, H 5.17, N 7.24, S 8.19.

In a similar manner by treatment **5b** with iodoacetamide with 83 % yield **7b** as yellow powder was obtained. M.p. 150 -152 °C (from ethanol). IR (ν/cm): 1660, 1692 (C=O); 3200, 3408 (NH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.48 (3H, s OMe); 3.51 and 3.73 (2H, d and d, J = 14 Hz, SCH_2); 4.62 and 5.32 (2H, d and d, J = 6.4 Hz, 4-H and 5-H); 7.1 – 7.5 (9H, complex, 4-C_6H_4 and 6-Ph); 7.58 and 7.98 (2H, br.s and br. s, $CONH_2$); 10.08 (1H, s, NH).). Anal. Calcd.for $C_{21}H_{19}ClN_2O_3S$: C 60.79, H 4.62, N 6.75, S 7.73. Found: C 60.59, H 4.57, N 6.72, S 7.80.

In a similar manner by treatment **5c** with iodoacetamide with 71 % yield **7c** as yellow powder was obtained. M.p. 179 –181 °C (from ethanol).). IR (ν/cm): 1664, 1682 sh (C=O); 3204, 3308, 3358, 3442 (NH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.48 (3H, s OMe); 3.57 and 3.79 (2H, d and d, J = 14 Hz, SCH_2); 4.83 and 5.40 (2H, d and d, J = 6.4 Hz, 4-H and 5-H); 7.3 – 8.2 (11H, complex, 4-C_6H_4, 6-Ph and $CONH_2$); 10.28 (1H, s, NH). Anal. Calcd.for $C_{21}H_{19}N_3O_5S$: C 59.28, H 4.50, N 9.88, S 7.54. Found: C 58.97, H 4.48, N 9.64, S 9.38.

Methyl 3-ethoxycarbonylmethyl-4,6-diphenyl-4,7-dihydrothiazolo[3,2-a]pyridine-8-carboxylate (8).

A mixture of thione **5a** (0,65 g, 2 mmol), 95% ethyl 4-chloroacetoacetate (0,50 ml, 2.5 mmol) and triethylamine (0.35 ml, 2.5 mmol) in 10 ml of methanol was refluxed for 30 min and stirred at ambient temperature for 24 hours. The precipitate was filtered and washed with 5 ml of cold ethanol, 20 ml of water and 5 ml of cold ethanol to give 0.80 g (46%) of **9** as yellow powder. M.p. 194-196°C (from ethanol). IR (ν/cm): 1663, 1732 (C=O); ^{1}H NMR ($CDCl_3$, δ, ppm): 1.08 and 3.96 (5H, t and q, OEt); 2.80 (2H, q, J = 17 Hz, CH_2); 3.68 (3H, s, OMe); 4.80 and 5.32 (2H, d and d, J = 7.0 Hz, 4-H and 5-H); 6.12 (1H, s, 2-H); 7.1 – 7.4 (10H, m, 4,6-Ph). Anal. Calcd.for $C_{25}H_{23}NO_4S$: C 69.26, H 5.35, N 3.23, S 7.40. Found: C 69.22, H 5.39, N 3.18, S 7.53.

References

1 V.P. Litvinov, Phosphorus, Sulfur Silicon Relat. Elem. **74**, 139 (1993)

2 A.A.Krauze, R.O.Vitolina, G.V.Zarinsh, et al., Khim.-Farm.Zh. (in Russian) **19**, 540 (1985); C.A. **104**, 68727 (1986)

3 A.A.Krauze, R.O.Vitolina, M.R.Romanova, G.Dubur, Khim.-Farm.Zh. (in Russian) **22**, 548 (1988); C.A. **109**, 149305 (1988)

4 A.A.Krauze, A.G.Odinecs, A.A.Verreva, et al., Khim.-Farm.Zh. (in Russian) **25**, 40 (1991); C.A. **115**, 223418 (1991)

5 I.E.Kirule, A.A.Krauze, A.H.Velena, et al., Khim.-Farm.Zh. (in Russian) **26**, 59 (1992); C.A. **119**, 72467 (1993)

6 D.Tirzite, A.Krauze, A.Zubareva, et al., Chem. Heterocycl. Comp. **38**, 795 (2002)

7. A.A.Krauze, Z.A.Bomika, A.M.Shestopalov, et al., Chem.Heterocycl.Comp. **17**, 279 (1981)

8. A.A.Krauze, Z.A.Bomika, Yu.E.Pelcher, et al., Chem.Heterocycl.Comp. **19**, 1202 (1983)

9. M. Hasegava, A.Nakayama, T.Hosokami et.al. Chem. Pharm. Bull. **43**, 78 (1995)

10. A.A.Krauze, E.E.Liepinsh, Yu.E.Pelcher, Z.A.Kalme, I.V.Dipans, G.Ya.Dubur.Chem. Heterocycl.Comp. **21**, 77 (1985)

11. J.Kuthan, P.Nesvadba, Z.Donnerova, P.Trška. Coll.Czech.Chem.Commun. **42**, 2152 (1977)

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