CONVENIENT ONE-POT SYNTHESIS OF 2-CARBAMOYLMETHYLTHIO-3-CYANO-4,6-DIARYL-5-ETHOXYCARBONYL-1,4-DIHYDROPYRIDINES

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Abstract: 2-Carbamoylmethylthio-3-cyano-4,6-diaryl-5-ethoxycarbonyl-1,4-dihydropyridines **1** were obtained by an one-pot condensation of ethyl 4-nitrobenzoylacetate, an aromatic aldehyde and cyanothioacetamide in the presence of piperidine with subsequent alkylation and dehydroxylation. Thorpe's cyclization of **1** yielded thieno[2,3-b]pyridines **3**.

Introduction

2-Alkylthio-3-cyano-1,4-dihydropyridines, which have been obtained by alkylation of 1,4-dihydropyridine-2-thiones [1,2], have revealed cardiovascular [3,4], antioxidant and hepatoprotective [5,6] activities. The corresponding 2-alkylthio-3-cyano-6-hydroxy-1,4,5,6-tetrahydropyridines exhibit tangible cardiovascular activity too [3], but, unfortunately, these compounds without strong electron withdrawing group at 5 position and sterically bulky group at 6 position are characterized as unstable compounds. They in course of preparation split off water molecule to give 2-alkylthio-1,4- or 4,5-dihydropyridines [7, 8].

In continuation of searching biologically active compounds we have elaborated convenient one-pot synthesis of 2-carbamoylmethylthio-3-cyano-4,6-diaryl-5-ethoxycarbonyl-1,4-dihydropyridines **1** and investigated their Thorpe's cyclization.

Results and discussion

Alkylation of 1,4-dihydropyridine-2(3H)-thiones bearing three nucleophilic reaction centres (S, 1-N and 3-C) at mild reaction conditions preceeded exclusively at sulphur atom [1,2]. Synthesis of 1,4-dihydropyridine-2(3H)-thiones bearing electron donating substituents in position 4 is rather complicated because they, being good antioxidants [9], in course of preparation and isolation oxidize to corresponding pyridine-2(1H)-thiones.

Convenient method of one-pot synthesis of 2-carbamoylmethylthio-3-cyano-4,6-diaryl-5-ethoxycarbonyl-1,4-dihydropyridines **1** (also bearing electron donating substituents in position 4) has been elaborated by condensation of ethyl 4-nitrobenzoylacetate, an aromatic aldehyde and cyanothioacetamide in the presence of piperidine with subsequent treatment with iodoacetamide and acidification. The yields were 64 – 70 %, only in case of **1c** it was 86 %.

Piperidinium 6-hydroxy-1,4,5,6-tetrahydropyridine-2-thiolates as primary intermediates have been isolated only in case of 4-phenyl substituent [10]. To carry out a one-pot condensation of ethyl 4-nitrobenzoylacetate, an aromatic aldehyde and cyanothioacetamide in the presence of piperidine with subsequent alkylation (without acidification) only in case of 4-phenyl substituent 2-carbamoylmethylthio-1,4,5,6-tetrahydropyridine **2** has been obtained. 2-carbamoylmethylthio-1,4-dihydropyridine **1a** was prepared also in 95 % yield by short heating of 2-carbamoylmethylthio-1,4,5,6-tetrahydropyridine **2** in HCl-ethanol solution.

Treatment of **1a-d** with KOH in water-ethanol solution gave thieno[2,3-b]pyridines **3a-d** (62 – 80 % yields) which means that next to the Thorpe's cyclization spontaneous oxidation of dihydropyridine cycle took place.

The structures of synthesized compounds were proved by spectroscopic methods. In the IR spectra characteristic absorption bands of 3-C=N group for dihydropyridines **1** and tetrahydropyridine **2** at 2194 – 2204 cm⁻¹ are observed, which disappeared by Thorpe's cyclization (in case of compounds **3**). Absorption 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 spectrum of **2** with J_{4,5} = 12 Hz according to [7] confirm a trans-diaxial configuration of the 4-H and 5-H protons. In case of 1,4-dihydropyridines **1**, the characteristic 4-H proton signals at 4.56 – 4.80 ppm are observed.

In conclusion a convenient method of one-pot synthesis of 2-carbamoylmethylthio-3-cyano-4,6-diaryl-5-ethoxycarbonyl-1,4-dihydropyridines **1** have been elaborated by condensation of ethyl 4-nitrobenzoylacetate, an aromatic aldehyde and cyanothioacetamide in the presence of piperidine with subsequent treatment with iodoacetamide and acidification. 2-Carbamoylmethylthio-3-cyano-6-hydroxy-1,4,5,6-tetrahydropyridine **2** as intermediate is isolated. The Thorpe's cyclization of **1** is supported by spontaneous oxidation of dihydropyridine cycle.

a) $\text{R} = \text{H}$; b) $\text{R} = \text{NO}_2$; c) $\text{R} = \text{OMe}$; d) $\text{R} = \text{OH}$

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 spectrometer. Chemical shifts are expressed in δ (p.p.m. downfield from TMS) and coupling constants (J) in Hertz. 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.

2-Carbamoylmethylthio-3-cyano-5-ethoxycarbonyl-6-(4-nitrophenyl)-4-phenyl-1,4-dihydro-pyridine 1a.

A mixture of ethyl 4-nitrobenzoate (1.19 g, 5 mmol), benzaldehyde (0.53 g, 5 mmol), cyanothioacetamide (0.5 g, 5 mmol) and piperidine (0.55 ml, 5.5 mmol) in 25 ml of ethanol was shortly heated until dissolution and stirred for 10 min at ambient temperature. Then to the reaction mixture iodoacetamide (1.02 g, 5.5 mmol) was added, shortly heated and stirred for 15 min

at the ambient temperature. Finally 5 ml of 3N hydrochloric acid in ethanol was added, refluxed for 5 min and stirred for 1 h at the ambient temperature. The precipitate was filtered and washed with 10 ml of ethanol, 10 ml of water to give 1.55 g (67 %) of **1a** as yellow crystals; mp 208 – 210°C. IR: 1680, 1708 (C=O), 2204 (C≡N); 3190, 3362 (NH, NH₂); ¹H NMR (DMSO-d₆): 0.75 (3H, t, CH₂CH₃); 3.65 and 3.90 (1H, d and d, J = 15 Hz, SCH₂); 3.75 (2H, q, CH₂CH₃); 4.66 (1H, s, 4-H); 7.3 – 7.4 (5H, m, 4-C₆H₅); 7.64 and 7.96 (2H, br. s and br. s, CONH₂), 7.75 and 8.28 (4H, d and d, 6-C₆H₄); 10.95 (1H, s, NH). Calcd. for C₂₃H₂₀N₄O₅S : C 59.47, H 4.51, N 12.06, S 6.90. Found C 59.54, H 4.37, N 11.95, S 6.90.

In a similar manner (4-nitrobenzaldehyde was used instead of benzaldehyde) **2-carbamoylmethylthio-3-cyano-4,6-di-(4-nitrophenyl)-5-ethoxycarbonyl-1,4-dihydropyridine 1b** was obtained (86 %) as slightly yellow powder, mp 203 – 205°C; IR: 1664, 1680 sh, 1696 (C=O); 2194 (C≡N); 3200, 3262, 3340, 3412 (NH, NH₂); ¹H NMR (DMSO-d₆): 0.72 (3H, t, CH₂CH₃); 3.64 (2H, q, CH₂CH₃); 3.60 and 3.92 (2H, d and d, J = 15 Hz, SCH₂); 4.80 (1H, s, 4-H); 7.62 and 8.22, 7.72 and 8.24 (8H, d and d, d and d, 4,6-C₆H₄) 7.68 and 7.96 (2H, s and s, CONH₂); 11.10 (1H, s, NH). Anal. Calcd. for C₂₃H₁₉N₅O₇S: C 54.22, H 3.76, N 13.75, S 6.29. Found C 54.11, H 3.82, N 13.68, S 6.08.

In a similar manner (4-methoxybenzaldehyde was used instead of benzaldehyde) **2-carbamoylmethylthio-3-cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-(4-nitrophenyl)-1,4-dihydropyridine 1c** (yield 64 %) was obtained as slightly yellow powder; mp 186-189°C. IR: 1686, 1708 (C=O); 2198 (C≡N); 3196, 3304, 3368 (NH, NH₂). ¹H NMR (DMSO-d₆): 0.74 (3H, t, CH₂CH₃); 3.60 and 3.84 (2H, d and d, J=15 Hz, SCH₂); 3.72 (2H, q, CH₂CH₃); 3.74 (1H, s, OCH₃); 4.56 (1H, m, 4-H); 4.94 and 7.22 (4H, br. s and br. s, 4-C₆H₄); 7.58 and 7.92 (2H, br. s, and br. s, CONH₂); 7.71 and 8.27 (4H, d and d, 6-C₆H₄); 10.86 (1H, s, NH). Anal. Calcd. for C₂₄H₂₂N₄O₆S: C 58.30; H 4.50; N 11.30; S 6.50. Found: C 58.19; H 4.44; N 11.28, S 6.62.

In a similar manner (4-hydroxybenzaldehyde was used instead of benzaldehyde) **2-carbamoylmethylthio-3-cyano-5-ethoxycarbonyl-4-(4-hydroxyphenyl)-6-(4-nitrophenyl)-1,4-dihydropyridine 1d** (yield 70 %) was obtained as colourless powder; mp 219 – 221°C. IR: 1666, 1680 (C=O); 2194 (C≡N); 3184, 3320, 3430 (NH, NH₂). ¹H NMR (DMSO-d₆): 0.72 (3H, t, CH₂CH₃); 3.62 and 3.86 (2H, d and d, J=15 Hz, SCH₂); 3.72 (2H, q, CH₂CH₃); 4.58 (1H, s, 4-H); 6.72 and 7.10 (4H, d and d, 4-C₆H₄); 7.57 and 7.90 (2H, br. s, and br. s, CONH₂), 7.68 and 8.23 (4H, d and d, 6-C₆H₄); 9.36 (1H, s, OH); 10.80 (1H, s, NH). Anal. Calcd. for C₂₃H₂₀N₄O₆S: C 57.49; H 4.20; N 11.66; S 6.67. Found: C 57.34; H 4.25; N 11.59; S 6.72.

2-Carbamoylmethylthio-3-cyano-5-ethoxycarbonyl-6-hydroxy-6-(4-nitrophenyl)-4-phenyl-1, 4, 5, 6-tetrahydropyridine 2.

A mixture of ethyl 4-nitrobenzoylacetate (1.19 g, 5 mmol), benzaldehyde (0.53 g, 5 mmol), cyanothioacetamide (0.5 g, 5 mmol) and piperidine (0.55 ml, 5.5 mmol) in 25 ml of ethanol was shortly heated until dissolution and stirred for 10 min at ambient temperature. Then to the reaction mixture iodoacetamide (1.02 g, 5.5 mmol) was added, shortly heated and stirred for 1 h at the ambient temperature. The precipitate was filtered and washed with 10 ml of ethanol, 10 ml of water to give 1.62 g (67 %) of **2** as slightly yellow crystals; mp 179 - 180°C. IR: 1676, 1705 (C=O); 2200 (C≡N); 3164, 3198, 3328, 3444, 3472 (NH, NH₂, OH). ¹H NMR (DMSO-d₆): 0.45 (3H, t, CH₂CH₃); 3.04 (1H, d, J=12 Hz, 5-H); 3.44 (2H, q, CH₂CH₃); 3.62 (2H, s, SCH₂); 4.12 (1H, d, J=12 Hz, 4-H); 6.80 (1H, s, OH); 7.25 (5H, m, 4-Ph); 7.50 and 7.90 (2H, br.s and br. s, CONH₂); 7.86 and 8.22 (4H, d and d, 6-C₆H₄); 9.32 (1H, s, NH). Anal. Calcd. for C₂₃H₂₂N₄O₆S: C 57.25; H 4.60; N 11.61; S 6.64. Found: C 57.41; H 4.55; N 11.57; S 6.70.

Dehydrogenation of 6-hydroxy-1, 4, 5, 6-tetrahydropyridine 2. 1, 4, 5, 6-Tetrahydropyridine **2** (0.48 g, 1 mmol) in 5 ml of 0.5 M HCl-ethanol solution was shortly heated till dissolution and stirred at ambient temperature for 30 min. The precipitate was filtered and washed with 5 ml of ethanol to give 0.44 g (95 %) of **1a** as yellow crystals; mp 208 - 210°C.

3-Amino-2-carbamoyl-5-ethoxycarbonyl-6-(4-nitrophenyl)-4-phenylthieno[2,3-b]pyridine 3a.

A mixture of dihydropyridine **1a** (0.93 g, 2 mmol) and 1 ml 4M KOH water solution in 20 ml of ethanol was refluxed for 10 min, stirred at ambient temperature for 30 min. The precipitate was filtered and washed with 20 ml of ethanol, 20 ml of water to give 0.68 g (73 %) of **3a** as yellow powder, mp 273 - 275°C. IR: 1658, 1716 (C=O); 3158, 3320, 3382, 3466 (NH₂); ¹H NMR (DMSO-d₆): 0.73 (3H, tt, CH₂CH₃); 3.81 (2H, qq, CH₂CH₃); 5.70 (2H, br.s, 3-NH₂); 7.3 - 8.5 (11H, complex, 4-C₆H₅, 6-C₆H₄ and 2-CONH₂). Anal. Calcd. for C₂₃H₁₈N₄O₅S: C 59.73; H 3.92; N 12.11; S 6.93. Found C 60.09; H 3.82; N 12.19; S 6.90.

In a similar manner by treatment dihydropyridine **1b** with KOH water solution in ethanol

3-amino-2-carbamoyl-4,6-di-(4-nitrophenyl)-5-ethoxycarbonylthieno[2,3-b]pyridine 3b as orange powder was obtained, yield 80 %, mp 227 - 230°C; IR: 1655, 1723 (C=O); 3170, 3322, 3468, 3490 (NH₂); ¹H NMR (DMSO-d₆): 0.72 (3H, t, CH₂CH₃); 3.82 (2H, q, CH₂CH₃); 5.52 and 5.60 (4H, br.s and br.s. 3-NH₂ and CONH₂); 7.86 and 8.32, 7.87 and 8.43 (8H, d and d, d and d, 4,6-C₆H₄). Anal. Calcd. for C₂₃H₁₇N₅O₇S: C 54.44; H 3.38; N 13.80; S 6.32. Found C 54.73; H 3.33; N 13.91; S 6.35. Found: C 54.17; H 3.20; N 13.60; S 6.17.

In a similar manner by treatment dihydropyridine **1c** with KOH water solution in ethanol

3-amino-2-carbamoyl-4-(4-methoxyphenyl)-6-(4-nitrophenyl)-5-ethoxycarbonyl-thieno[2,3-b]pyridine 3c as orange powder was obtained, yield 70 %, mp 269 - 272°C; IR: 1654, 1729 (C=O); 3142, 3320, 3460 (NH₂); ¹H NMR (DMSO-d₆): 0.78 (3H, t, CH₂CH₃); 3.80 (2H, q, CH₂CH₃); 3.82 (3H, s, OMe); 5.80 (2H, br.s 3-NH₂); 7.0 – 8.6 (10H, complex, 4,6-C₆H₄ and CONH₂). Anal. Calcd. for C₂₄H₂₀N₄O₆S: C 58.53, H 4.09, N 11.38, S 6.51. Found C 58.81, H 3.99, N 11.42, S 6.59.

In a similar manner by treatment dihydropyridine **1d** with KOH water solution in ethanol

3-amino-2-carbamoyl-4-(4-hydroxyphenyl)-6-(4-nitrophenyl)-5-ethoxycarbonyl-thieno[2,3-b]pyridine 3d as orange powder was obtained, yield 62 %, mp 276 - 278°C; IR: 1646, 1718 (C=O); 3326, 3412, 3430 (OH, NH₂); ¹H NMR (DMSO-d₆): 0.84 (3H, t, CH₂CH₃); 3.86 (2H, q, CH₂CH₃); 6.10 (2H, br.s 3-NH₂); 6.60 and 6.97 (4H, d and d, 4-C₆H₄); 7.25 (2H, br.s, CONH₂); 7.90 and 8.30 (4H, d and d, 6-C₆H₄); 8.35 (1H, s, OH). Anal. Calcd. for C₂₃H₁₈N₄O₆S: C 57.74, H 3.79, N 11.71, S 6.70. Found C 54.47, H 3.62, N 11.53, S 6.54.

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