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

A.Krauze*, L.Sīle, G.Dubur
Latvian Institute of Organic Synthesis, Riga, Aizkraukles 21, LV-1006, Latvia; krauze@osi.lv

Abstract: 2-Carbamoylmethylthio-3-cyano-4,6-diaryl-5-etfioxycarbonyl-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 elabolarated 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.

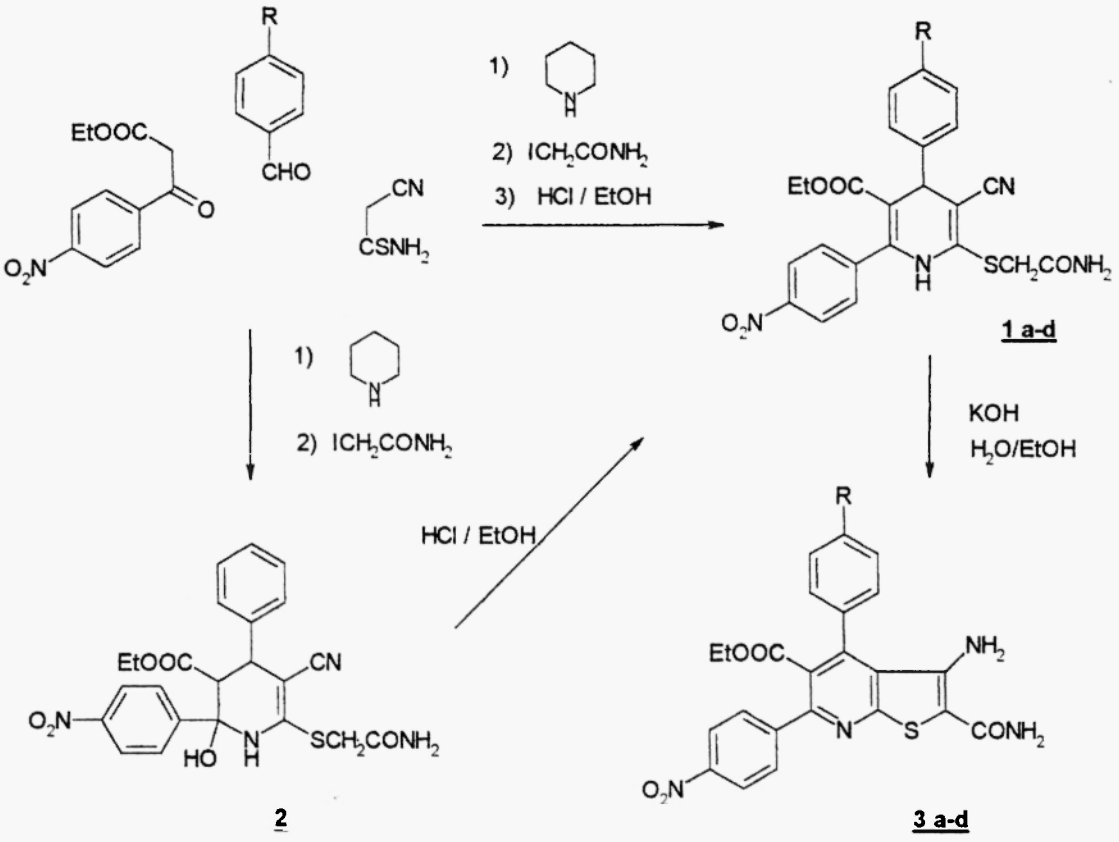
Convenient method of one-pot synthesis of 2-carbamoylmethylthio-3-cyano-4,6-diaryl-5-ethoxycarbonyl-1,4-dihydropyridines **1** (also bearing electron donating substituents in position 4) has been elaborated by condensation of ethyl 4-nitrobenzoylacetate, an aromatic aldehyde and cyanothioacetamide in 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 absorbtion 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**). 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 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-Carbamoylmethyllthio-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) R = H; b) R = NO_2; c) R =OMe; d) R=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-dihydropyridine 1a. 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 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, NH_2); ^{1}H NMR (DMSO-d_6): 0.75 (3H, t, $CH_2\underline{CH_3}$); 3.65 and 3.90 (1H, d and d, J = 15 Hz, SCH_2); 3.75 (2H, q, $\underline{CH_2}CH_3$); 4.66 (1H, s, 4-H); 7,3 – 7.4 (5H, m, 4-C_6H_5); 7.64 and 7.96 (2H, br. s and br. s, $CONH_2$), 7.75 and 8.28 (4H, d and d, 6-C_6H_4); 10.95 (1H, s, NH). Calcd.for $C_{23}H_{20}N_4O_5S$: 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, NH_2); ^{1}H NMR (DMSO-d_6): 0.72 (3H, t, $CH_2\underline{CH_3}$); 3.64 (2H, q, $\underline{CH_2}CH_3$); 3.60 and 3.92 (2H, d and d, J = 15 Hz, SCH_2); 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-C_6H_4) 7.68 and 7.96 (2H, s and s, $CONH_2$); 11.10 (1H, s, NH). Anal. Calcd.for $C_{23}H_{19}N_5O_7S$: 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, NH_2). ^{1}H NMR (DMSO-d_6,): 0.74 (3H, t, $CH_2\underline{CH_3}$); 3.60 and 3.84 (2H, d and d, J=15 Hz, SCH_2); 3.72 (2H, q, $\underline{CH_2}CH_3$); 3.74 (1H, s, $0\underline{CH_3}$); 4.56 (1H, m, 4-H); 4.94 and 7.22 (4H, br. s and br. s, 4-C_6H_4); 7.58 and 7.92 (2H, br. s, and br. s, $CONH_2$); 7.71and 8.27 (4H, d and d, 6-C_6H_4); 10.86 (1H, s, NH). Anal. Calcd. for $C_{24}H_{22}N_4O_6S$: 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, NH_2). ^{1}H NMR (DMSO-d_6,): 0.72 (3H, t, $CH_2\underline{CH_3}$); 3.62 and 3.86 (2H, d and d, J=15 Hz, SCH_2); 3.72 (2H, q, $\underline{CH_2}CH_3$); 4.58 (1H, s, 4-H); 6.72 and 7.10 (4H, d and d, 4-C_6H_4); 7.57and 7.90 (2H, br. s, and br. s, $CONH_2$), 7.68 and 8.23 (4H, d and d, 6- C_6H_4); 9.36 (IH, s, OH); 10.80 (1H, s, NH). Anal. Calcd. for $C_{23}H_{20}N_4O_6S$: 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, NH_2, OH). ^{1}H NMR (DMSO-d_6): 0.45 (3H, t, $CH_2\underline{CH_3}$); 3.04 (1H, d, J=12 Hz, 5-H); 3.44 (2H, q, $\underline{CH_2}CH_3$); 3.62 (2H, s, SCH_2); 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, $CONH_2$); 7.86 and 8.22 (4H, d and d, 6-C_6H_4); 9.32 (1H, s, NH). Anal. Calcd. for $C_{23}H_{22}N_4O_6S$: 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 (NH_2); ^{1}H NMR (DMSO-d_6): 0.73 (3H, tt, CH_2CH_3); 3.81 (2H, qq, CH_2CH_3); 5.70 (2H, br.s, 3-NH_2); 7.3 – 8.5 (11H, complex, 4-C_6H_5, 6-C_6H_4 and 2-$CONH_2$). Anal. Calcd.for $C_{23}H_{18}N_4O_5S$: 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 (NH_2); ^{1}H NMR (DMSO-d_6): 0.72 (3H, t, $CH_2\underline{CH_3}$), 3.82 (2H, q, $\underline{CH_2}CH_3$); 5.52 and 5.60 (4H, br.s and br.s. 3-NH_2 and $CONH_2$); 7.86 and 8.32, 7.87 and 8.43 (8H, d and d, d and d, 4,6-C_6H_4). Anal. Calcd.for $C_{23}H_{17}N_5O_7S$: 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 (NH_2); ^{1}H NMR (DMSO-d_6): 0.78 (3H, t, $CH_2\underline{CH_3}$); 3.80 (2H, q, $\underline{CH_2}CH_3$); 3.82 (3H, s, OMe); 5.80 (2H, br.s 3-NH_2); 7.0 – 8.6 (10H, complex, 4,6-C_6H_4 and $CONH_2$). Anal. Calcd.for $C_{24}H_{20}N_4O_6S$: 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, NH_2); ^{1}H NMR (DMSO-d_6): 0.84 (3H, t, $CH_2\underline{CH_3}$); 3.86 (2H, q, $\underline{CH_2}CH_3$); 6.10 (2H, br.s 3-NH_2); 6.60 and 6.97 (4H,d and d, 4-C_6H_4); 7.25 (2H, br.s, $CONH_2$); 7.90 and 8.30 (4H, d and d, 6-C_6H_4); 8.35 (1H, s, OH). Anal. Calcd.for $C_{23}H_{18}N_4O_6S$: 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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