SYNTHESIS OF 6- ALKOXYCARBONYLMETHYL SULFANYL-5-CYANO-2-METHYL-4-PHENYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLATES

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Abstract: 6-Alkoxycarbonylmethylsulfanyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylates **3** as a more lipophilic derivatives of the biologically active 6-methylsulfanyl-1,4-DHP-3-carboxylates **2** have been prepared by the alkylation of 1,4-dihydropyridine-6-thiolates **1** with alkyl bromoacetates. Reactivity of **2** with KOH/H_2O was investigated.

Introduction

1,4–Dihydropyridines (DHPs) are known as effective calcium channel effectors, especially antagonists. Many cardiovascular drugs which are currently in the clinics or are in different stages of development are based on DHPs[1-4]. Pharmacology of DHPs is at the eve of a novel boom: after synthesis, studies, development of a set of antihypertensive and antianginal drugs, the interest is growing towards pharmacological activities not connected (or partially connected) with their calcium antagonist properties: neurotropic (antiamnesic, anticonvulsant, neuroregulatory)[5], membrane protecting[6-8], analgesic[9], antidiabetic[10], antiinflammatory[11], gene-transfection agents[12] and also as uroselective agents for benign prostatic hyperplasia treatment[13].

6-Alkylsulfanyl-1,4-DHPs display cardiovascular[14-16], hepatoprotective[17], antioxidant[18], and antiradical[19] activities, however, these compounds are still insufficiently studied. As we have shown recently, ethyl 4-aryl-5-cyano-2-methyl-6-methylsulfanyl-1,4-DHP-3-carboxylates besides being of low toxicity display antihypertensive or vasodilating activities[20] depending on the character of the substituents in the position 4, but to optimize lipophilicity, another ester group has to be introduced in the 1,4-DHP molecule[1]. 6-Alkoxycarbonylmethylsulfanyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylates bearing two ester groups could be interesting from this point of view.

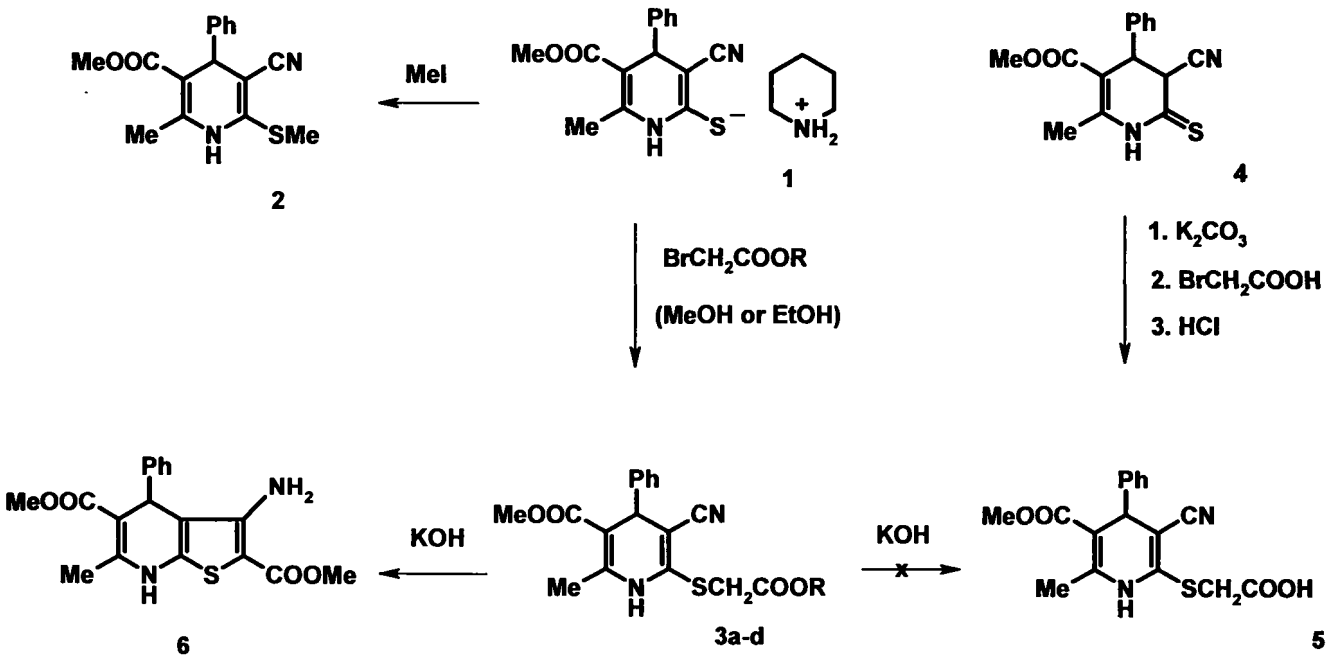
Results and discussion

The task of this publication is the synthesis of new 1,4-DHPs containing lipophilic alkoxycarbonylmethylsulfanyl group at the position 6 as the group which might undergo further chemical transformations.

3-Ethoxycarbonyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-6-thiolate **1** was prepared by one-pot four-component condensation of ethyl acetoacetate, benzaldehyde, 2-cyanothioacetamide and piperidine[21]. Alkylation of thiolate **1** with iodomethane (50 % excess) and alkyl bromoacetate (5-10 % excess) gave rise to methyl 5-cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylate **2** and methyl 6-alkoxycarbonylmethylsulfanyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylates **3**.

a) R = Me; b) R = Et; c) R = i-Pr; d) R = *t*-Bu

Our efforts to prepare methyl 6-benzyloxycarbonylmethylsulfanyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate **3e** under the above mentioned reaction conditions were not successful. Alkylation of thiolate **1** with benzyl



2-bromoacetate in anhydrous benzyl alcohol gave rise to an unstable product which by washing with ethanol easily underwent transesterification to give ethyl carboxylate **3b**.

Hydrolysis of ester **3a** with KOH/H_2O to the corresponding acid **5** was not successful, as the Thorpe's cyclisation occurs instead of hydrolysis to form 3-amino-4,7-dihydrothieno[2,3-b]pyridine **6**. Carboxylic acid **5** was prepared by alkylation of thione **4**[21] with bromoacetic acid in the presence of excess of K_2CO_3 with subsequent careful neutralization of the reaction mixture.

The structures of the compounds are proved by spectroscopic methods. In the IR spectra of 1,4-DHPs **2**, **3** and **5** absorption bands for $\nu_{C\equiv N}$ at 2197-2201 cm^{-1} (disappear in the case of thienopyridines **6**) and bands corresponding to the type of conjugation for $\nu_{C=O}$ are seen. In the ^1H NMR spectra of **2**, **3** and **5** the most characteristic are singlets of 4-H protons at 4.51 - 5.00 ppm. In the case of **3** and **5** AB-doublets of the SCH_2 group with J = 15.6 - 16.0 Hz are seen.

In conclusion, a series of 6-alkoxycarbonylmethylthio-5-cyano-2-methyl-4-phenyl-1,4-DHP-3-carboxylates **3** which are more lipophilic derivatives of the biologically active 6-methylthio-1,4-DHP-3-carboxylate **2** have been prepared by alkylation of 1,4-DHP-6-thiolates with alkyl bromoacetates. By treatment of **3a** with KOH/H_2O the corresponding 3-amino-4,7-dihydrothieno[2,3-b]pyridine **6** was prepared.

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 Varian Mercury-200 (200 MHz) spectrometer. 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.

Methyl 5-cyano-2-methyl-6-methylthio-4-phenyl-1,4-dihydropyridine-3-carboxylate 2: A mixture of thiolate **1** (0.37 g, 10 mmol) and methyl iodide (0.12 ml, 20 mmol) in 20 ml of methanol was shortly heated until dissolution of thiolate **1** and stirred at ambient temperature for 1h. The precipitate was filtered, washed with 5 ml of cold (ca. 5°C) methanol and 20 ml of water to give ester **2** as colourless crystals, yield 87 %, mp 163 - 164°C. IR: 1638, 1698 (C=O); 2200 (C≡N); 3392 (NH). ^1H NMR ($CDCl_3$): 2.38 (s, 3H, 2-CH_3); 2.47 (s, 3H, SCH_3); 3.68 (s, 3H, OCH_3); 4.70 (s, 1H, 4-H); 6.20 (s, 1H, NH); 7.1 - 7.4 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$ - DMSO-d_6): 16.03 (q); 18.08 (q); 41.73 (d); 50.55 (q); 88.99 (s); 100.24 (s); 118.92 (s); 126.57, 127.53, 128.31, 144.38 (aromatic C); 144.90 (s), 145.85 (s); 166.74 (s). Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C 63.97, H 5.37, N 9.33; Found: C 64.40, H 5.46, N 9.53.

General procedure for synthesis of 6-alkoxycarbonylmethylthio-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylates 3.

A mixture of 10 mmol of corresponding thiolate **1** and 11 mmol of alkyl bromoacetate in 20 - 25 ml of methanol (or ethanol) was shortly heated until dissolution of thiolate **1** and stirred at ambient temperature for 1 - 2 hr. The precipitated crystals (in case of **3c,d** 1 ml of water was added) were removed by filtration, washed with 10 ml of cold (ca. 5°C) ethanol and 20 ml of water to give 77 - 97% of 6-alkoxycarbonylmethylthio-1,4-dihydropyridine-3-carboxylates **3**.

Methyl 5-cyano-6-methoxycarbonylmethylthio-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 3a: colourless crystals, yield 96%, mp 122 - 123°C. IR: 1681, 1714 (C=O); 2197(C≡N); 3194, 3233, 3264 (NH). ^1H NMR ($CDCl_3$): 2.40 (s, 3H, 2-CH_3); 3.53 and 3.57 (d and d, J = 16.0 Hz, 2H, SCH_2); 3.59 (s, 3H, 3-$COOCH_3$); 3.81 (s, 3H, SCH_2COOCH_3); 4.66 (s, 1H, 4-H); 7.2 - 7.3 (m, 5H, C_6H_5); 8.40 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 19.48 (q); 34.86 (t); 42.37 (d); 51.29 (q); 53.76 (q); 91.54 (s); 101.55 (s); 118.60 (s); 127.20, 127.33, 128.73, 141.73 (aromatic C); 144.33 (s); 145.04 (s); 167.27 (s); 173.11 (s). Anal. Calcd. for $C_{18}H_{18}N_2O_4S$: C 60.32, H 5.06, N 7.82; Found: C 60.57, H 5.10, N 8.00.

Methyl 3-Cyano-6-ethoxycarbonylmethylthio-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 3b: colourless crystals, yield 97%, mp 136 - 137°C. IR: 1682, 1706 (C=O); 2197 (C≡N); 3194, 3234, 3263 (NH). ^1H NMR ($CDCl_3$): 1.32 (t, J = 7 Hz, 3H, CH_2CH_3); 2.40 (s, 3H, 2-CH_3); 3.52 and 3.55 (d and d, J = 16 Hz, 2H, SCH_2); 3.59 (s, 3H, OCH_3); 4.27 (q, J = 7 Hz, 2H, CH_2CH_3); 4.67 (s, 1H, 4-H); 7.2 - 7.4 (m, 5H, 4-C_6H_5); 8.56 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.01 (q); 19.47 (q); 35.07 (t); 42.35 (d); 51.28 (q); 63.25 (t); 91.25 (s); 101.52 (s); 118.62 (s); 127.29, 127.34, 128.65, 141.47 (aromatic C); 144.53 (s); 144.72 (s); 166.78 (s); 173.09 (s). Anal. Calcd. for $C_{19}H_{20}N_2O_4S$: C 61.27, H 5.41, N 7.52; Found: C 61.65, H 5.49, N 7.68.

Methyl 5-cyano-6-isopropoxycarbonylmethylthio-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 3c: colourless crystals, yield 77 %, mp 112 - 113°C. IR: 1645, 1685, 1696 (C=O); 2198 (C≡N); 3188, 3234, 3261 (NH). ^{1}H NMR ($CDCl_3$): 1.30 and 1.33 [s and s, 6H, CH($\underline{CH_3}$)$_2$]; 2.41 (s, 3H, 2-CH_3); 3.49 and 3.53 (d and d, J = 16 Hz, 2H, SCH_2); 3.60 (s, 3H, OCH_3); 4.68 (s, 1H, 4-H); 5.10 [m, 1H, $\underline{CH}(CH_3)_2$]; 7.1 - 7.4 (m, 5H, 4-C_6H_5); 8.63 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 19.47 (q); 21.61 (q); 35.32 (t); 42.34 (d); 51.27 (q); 71.64 (d); 90.99 (s); 101.48 (s); 118.68 (s); 127.20, 127.29, 128.71, 141.84 (aromatic C); 144.40 (s); 145.13 (s); 167.32 (s); 172.25 (s). Anal. Calcd. for $C_{20}H_{22}N_2O_4S$: C 62.15, H 5.74, N 7.25; Found: C 62.53, H 5.74, N 7.21.

Methyl 6-*tert*-Butoxycarbonylmethylthio-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 3d: colourless crystals, yield 86 %, mp 94 - 95°C. IR: 1645, 1684, 1700 sh (C=O); 2201 (C≡N); 3186, 3232, 3264 (NH). ^{1}H NMR ($CDCl_3$): 1.52 [s, 9H, C(CH_3)$_3$]; 2.40 (s, 3H, 2-CH_3); 3.44 and 3.48 (d and d, J = 16 Hz, 2H, SCH_2); 3.60 (s, 3H, OCH_3); 4.67 (s, 1H, 4-H); 7.1 - 7.4 (m, 5H, 4-C_6H_5); 8.68 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 19.47 (q); 27.87 (q); 36.23 (t); 42.31 (d); 51.26 (q); 84.61 (s); 90.71 (s); 101.42 (s); 118.75 (s); 127.19, 127.26, 128.70, 142.08 (aromatic C); 144.43 (s); 145.19 (s); 167.35 (s); 171.96 (s). Anal. Calcd. for $C_{21}H_{24}N_2O_4S$: C 62.98, H 6.04, N 7.00; Found: C 63.18, H 6.03, N 6.91.

Methyl 6-carboxymethylthio-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 5.
A mixture of 10 mmol of thione **4**, 20 mmol of dried and well crushed potassium carbonate and 15 mmol of bromoacetic acid in 100 ml of methanol was heated for 3 - 5 min at 50 - 60°C with stirring, and left for 20 hr at the ambient temperature. Then the insoluble part of potassium carbonate was separated by filtration, the reaction mixture neutralised with 1.5 N HCl solution in ethanol and precipitated sodium chloride was separated by filtration. Water (200 ml) was added and reaction mixture was acidified until pH 2 - 2.5. After 3-4 hr the precipitate was separated by filtration to give 63 % of acid **5a:** colourless crystals, yield 63%, mp 145 - 146 °C. IR: 1645, 1720 (C=O); 2200 (C≡N); 3191, 3256, 3450 sh (NH, OH). ^{1}H NMR (DMSO-d_6): 2.31 (s, 3H, 2-CH_3); 3.53 (s, 3H, OCH_3); 3.83 and 3.93 (d and d, J = 15.6 Hz, 2H, SCH_2); 4.51 (s, 1H, 4-H); 7.1 - 7.4 (m, 5H, 4-C_6H_5); 9.57 (s, 1H, NH); 13.01 (br.s, 1H, OH). ^{13}C NMR (DMSO-d_6): 18.12 (q); 34.35 (q); 41.89 (4-H); 50.97 (q); 89.70 (s); 100.27 (s); 118.92 (s); 126.82, 127.06, 128.66, 142,54 (aromatic C); 144.93 (s); 146.05 (s); 166.71 (s); 169.79 (s). Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: C 59.29, H 4.68, N 8.14; Found: C 59.15, H 4.60, N 8.20.

Dimethyl 3-Amino-6-methyl-4-phenyl-4,7-dihydrothieno[2,3-b]pyridine-2,5-dicarboxylate 6. A sample of 5-cyano-6-methoxycarbonylmethylthio-1,4-dihydropyridine **3** (0.72 g, 2 mmol) in 5 ml of methanol was treated with 1 ml of 2 M KOH water solution by short heating till reflux and stirring at room temperature for 1 hr. The precipitate was separated by filtration, washed with 2 ml of cold (ca. 5°C) methanol and 10 ml of water to yield 0.67 g (93 %) of **6** as light yellow powder, mp 261 - 262°C. IR: 1653, 1670 (C=O); 3310, 3364, 3480 (NH, NH_2). ^{1}H NMR ($CDCl_3$): 2.38 (s, 3H, 6-CH_3); 3.61 (s, 3H, 5-$COOCH_3$); 3.74 (s, 3H, 2-$COOCH_3$); 5.00 (s, 1H, 4-H); 5.27 (br.s, 2H, 3-NH_2); 6.24 (s, 1H, 7-NH); 7.1 - 7.3 (m, 5H, 4-C_6H_5). ^{13}C NMR (DMSO-d_6): 19.24 (q); 40.74 (d); 50.47 (q); 50.57 (q); 100.04 (s); 110.95 (s); 126.13, 127.36, 128.02, 142.27 (aromatic C); 146.65 (s); 146.78 (s); 152.50 (s); 164.11 (s); 167.42 (s). Anal. Calcd. for $C_{18}H_{18}N_2O_4S$: C 60.32, H 5.06, N 7.82; Found: C 60.48, H 5.00, N 7.74.

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