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SYNTHESIS OF 4-BENZO[1,3]DIOXOL-5-YLTHIENO-[2,3-*b*]PYRIDINES

S. Grinberga[1,2], A. Krauze[1], L. Krasnova[1], G. Duburs[1]

[1]Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., Riga, LV-1006, Latvia
[2]Riga Technical University, 14/24 Azenes Str., Riga, LV-1048, Latvia
e-mail: signe992@gmail.com

4,7-Dihydrothieno[2,3-*b*]pyridine **4** and thieno[2,3-*b*]pyridine **6** were obtained by Thorpe–Ziegler cyclization. $Mn(OAc)_3$/acetic acid system had been used for oxidation of 1,4-dihydropyridine **3** to pyridine derivative **5**. 6-Carbamoylmethylsulfanyl-1,4-dihydropyridine **3** was prepared by alkylation of piperidinium 1,4-dihydropyridine-2-thiolate **1** with iodoacetamide.

Key words: *piperidinium 1,4-dihydropyridine-2-thiolate, 6-thioxo-1,4,5,6-tetrahydropyridines, 6-alkylsulfanyl-1,4-dihydropyridines, 6-alkylsulfanylpyridines, 4,7-dihydrothieno[2,3-b]pyridines, thieno[2,3-b]pyridines, Thorpe–Ziegler cyclization.*

INTRODUCTION

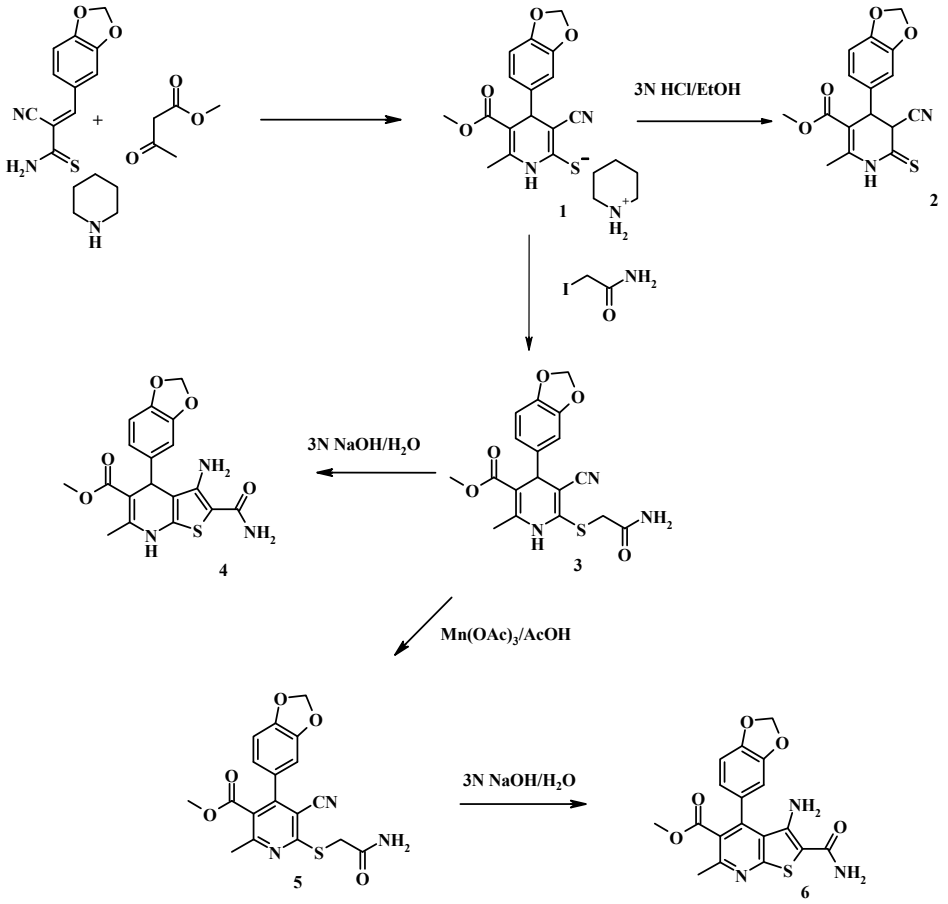
Thieno[2,3-*b*]pyridine derivatives are characterized by a very broad spectrum of biological activities. Some of them possess cytotoxic [1–4], antiinflammatory [5, 6], antiviral [7], antibacterial [8, 9] activity. Others are useful as hypolipoproteinemic and antiatherosclerotic agents [10] and inhibitors of mitogen-activated protein kinase enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, proliferative and nociceptive conditions [11]. On the other hand, 6-alkylsulfanylpyridine derivative containing benzo[1,3]dioxol-5-yl group (LUF 5853) is an adenosine (A1) receptor agonist [12].

In view of all these facts, we undertook synthesis of benzo[1,3]dioxol-5-yl group containing 6-alkylsulfanyl-1,4-dihydropyridine, 6-alkylsulfanylpyridine, 4,7-dihydrothieno[2,3-*b*]pyridine and thieno[2,3-*b*]pyridine for future studies of biological activities.

EXPERIMENTAL

All reagents were purchased from *Aldrich* or *Acros* and used without further purification. Melting points were determined on *OptiMelt MPA100* apparatus and were uncorrected. IR spectra had been recorded on a *„Shimadzu" IRPrestige-21* spectrometer (in nujol) and peak positions ν_{max} were expressed in cm^{-1}. ^1H NMR spectra were recorded on a *Varian Mercury-400* spectrometer (400 MHz). Chemical shifts are reported in ppm relative to HMDSO. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The coupling constants are expressed in Hz. Elemental analyses were performed on an *EA 1106* (*Carlo Erba Instrument*). 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.



Piperidinium 4-benzo[1,3]dioxol-5-yl-3-cyano-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine-2-thiolate (1)

Mixture of 3-benzo[1,3]dioxol-5-yl-2-cyanothioacrylamide (2.32 g, 10.0 mmol), methyl acetoacetate (1.16 g, 10.0 mmol) and piperidine (1.0 ml, 10.0 mmol) in ethanol (25 ml) was stirred at room temperature for 1 h. The precipitate was filtered and washed with 5 ml of ethanol and 5 ml of water to give 2.62 g (63%) of compound **1** as yellow solid; m.p. 167–169 °C. IR spectrum, ν, cm^{-1}: 1694 (C=O), 2182 (C≡N), 3258 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.47–1.61 and 2.93–2.96 (10H, m and m, $\underline{C_5H_{10}}NH_2^+$); 2.14 (3H, s, 6-Me); 3.40 (3H, s, OMe); 4.11 (1H, s, 4-H); 5.86 (2H, s, OCH_2O); 6.48–6.69 (3H, m, Ar); 8.14 (1H, s, NH); 8.20 (2H, br.s, $C_5H_{10}\underline{NH_2}^+$). Found, %: C 60.44; H 6.22; N 9.93. Calculated for $C_{21}H_{25}N_3O_4S$, %: C 60.70; H 6.06; N 10.11.

Methyl 4-benzo[1,3]dioxol-5-yl-5-cyano-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2)

To the solution of thiolate **1** (0.42 g, 1.0 mmol) in ethanol (10 ml) 0.6 ml of 3 *N* hydrochloric acid in ethanol were added and stirred for 0.5 h at room

temperature. The precipitate was filtered and washed with 5 ml of ethanol and 5 ml of water to give 0.25 g (76%) of compound **2** as yellow solid; m.p. 197–199 °C. IR spectrum, ν, cm^{-1}: 1686 (C=O), 2252 (C≡N), 3272 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.42 and 2.49 (2.4H and 0.6H, s and s, *cis*- and *trans*- 2-Me); 3.63 and 3.64 (2.4H and 0.6H, s and s, *cis*- and *trans*- OMe); 4.09 and 4.34 (0.2H and 0.2H, d and d, $J_{4,5}$ = 2 Hz, *trans*- 4-H and 5-H); 4.14 and 4.27 (0.8H and 0.8 H, d and d, $J_{4,5}$ = 6 Hz, *cis*- 4-H and 5-H); 5.88 (2H, s, OCH_2O); 6.49–6.71 (3H, m, Ar); 8.68 (1H, br.s, NH). Found, %: C 58.12; H 4.28; N 8.58. Calculated for $C_{16}H_{14}N_2O_4S$, %: C 58.17; H 4.27; N 8.48.

Methyl 4-benzo[1,3]dioxol-5-yl-6-carbamoylmethylsulfanyl-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylate (3)

To the solution of thiolate **1** (1.66 g, 4.0 mmol) in ethanol (15 ml) iodoacetamide (0.74 g, 4.0 mmol) was added and reaction mixture was heated for 5 min, then stirred for 1 h at room temperature. The precipitate was filtered and washed with 5 ml of ethanol and 5 ml of water to give 1.08 g (70%) of compound **3** as colourless solid; m.p. 202–204 °C. IR spectrum, ν, cm^{-1}: 1674; 1703 (C=O); 2193 (C≡N); 3170; 3354 (NH, NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.24 (3H, s, 2-Me); 3.47 (3H, s, OMe); 3.64 (2H, ABq, *J* = 15 Hz, SCH_2); 4.37 (1H, s, 4-H); 5.93 (2H, s, OCH_2O); 6.54–6.80 (3H, m, Ar); 7.54 and 7.85 (1H and 1H, br.s and br.s, $CONH_2$); 10.33 (1H, s, NH). Found, %: C 55.74; H 4.38; N 10.76. Calculated for $C_{18}H_{17}N_3O_5S$, %: C 55.81; H 4.42; N 10.85.

Methyl 3-amino-4-benzo[1,3]dioxol-5-yl-2-carbamoyl-6-methyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate(4)

To the solution of 1,4-dihydropyridine derivative **3** (0.19 g, 0.5 mmol) in ethanol (5 ml) 0.17 ml of 3 *N* sodium hydroxide in water were added. Then reaction mixture was heated for 5 min and stirred for 1 h at room temperature. The precipitate was filtered and washed with 1 ml of ethanol and 1 ml of water to give 0.16 g (84%) of compound **4** as yellow solid; m.p. 179–181 °C. IR spectrum, ν, cm^{-1}: 1637; 1655 (C=O); 3322; 3445; 3500 (NH, NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.23 (3H, s, 6-Me); 3.46 (3H, s, OMe); 4.86 (1H, s, 4-H); 5.86 (2H, s, OCH_2O); 6.25 (2H, s, NH_2); 6.46 (2H, s, $CONH_2$); 6.63–6.89 (3H, m, Ar); 9.70 (1H, s, NH). Found, %: C 55.88; H 4.23; N 10.76. Calculated for $C_{18}H_{17}N_3O_5S$, %: C 55.81; H 4.42; N 10.85.

Methyl 4-benzo[1,3]dioxol-5-yl-6-carbamoylmethylsulfanyl-5-cyano-2-methylpyridine-3-carboxylate (5)

To the solution of 1,4-dihydropyridine derivative **3** (0.39 g, 1.0 mmol) in acetic acid (15 ml) manganese (III) acetate dihydrate (0.54 g, 2.0 mmol) was added. Reaction mixture was refluxed for 2 h, cooled to room temperature and extracted with ethyl acetate, and dried over $MgSO_4$. Solvent was evaporated under reduced pressure and resulting oil was recrystallized from ethanol. The precipitate was filtered and washed with 5 ml of ethanol and 5 ml of water to give 0.28 g (73%) of compound **5** as white solid; m.p. 137–139 °C. IR spectrum, ν, cm^{-1}: 1688; 1712 (C=O); 2221 (C≡N); 3181; 3301 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.47 (3H, s, 2-Me); 3.53 (3H, s, OMe); 3.95 (2H, s, SCH_2); 6.08 (2H, s, OCH_2O); 6.75–7.01 (3H, m, Ar); 7.15 and 7.58 (1H and

1H, two br.s, $CONH_2$). Found, %: C 55.87; H 3.85; N 10.76. Calculated for $C_{18}H_{15}N_3O_5S$, %: C 56.10; H 3.92; N 10.90.

Methyl 3-amino-4-benzo[1,3]dioxol-5-yl-2-carbamoyl-6-methyl-thieno[2,3-*b*]pyridine-5-carboxylate (6)

To the solution of pyridine derivative **5** (0.19 g, 0.5 mmol) in ethanol (5 ml), 0.17 ml of 3 *N* sodium hydroxide in water were added. Then reaction mixture was heated for 5 min and stirred for 1 h at room temperature. The precipitate was filtered and washed with 1 ml of ethanol and 1 ml of water to give 0.17 g (87%) of compound **6** as yellow solid; m.p. 238–240 °C. IR spectrum, ν, cm^{-1}: 1654; 1730 (C=O); 3156; 3318; 3455 (NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.49 (3H, s, 6-Me); 3.50 (3H, s, OMe); 5.77 (2H, br.s, NH_2); 6.07 (2H, d, J = 5 Hz, OCH_2O); 6.72–7.01 (3H, m, Ar); 7.16 (2H, br.s, $CONH_2$). Found, %: C 56.05; H 3.66; N 10.56. Calculated for $C_{18}H_{15}N_3O_5S$, %: C 56.10; H 3.92; N 10.90.

RESULTS AND DISCUSSION

The aim of this work was to obtain a new potentially active 1,4-dihydropyridine, pyridine and thieno[2,3-*b*]pyridine derivatives containing benzo[1,3]-dioxol-5-yl group for future structure – activity studies.

Piperidinium 4-benzo[1,3]dioxol-5-yl-1,4-dihydropyridine-2-thiolate **1** was obtained by three-component condensation of benzo[1,3]dioxol-5-yl-2-cyanothioacrylamide, methyl acetoacetate and piperidine in 63% yield. 4-Benzo[1,3]-dioxol-5-yl-6-thioxo-1,4,5,6-tetrahydropyridine **2** was prepared in 76% yield by acidification of thiolate **1** with HCl/EtOH solution. 6-Carbamoylmethylsulfanyl-5-cyano-1,4-dihydropyridine **3** was obtained in 70% yield by alkylation of 1,4-dihydropyridine-2-thiolate **1** with iodoacetamide. The treatment of 6-carbamoylmethylsulfanyl-5-cyano-1,4-dihydropyridine **3** with $NaOH/H_2O$ gave the desired 3-amino-4-benzo[1,3]dioxol-5-yl-2-carbamoyl-6-methyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid methyl ester (**4)** in 84% yield. The manganese (III) acetate/acetic acid system was used for oxidation of 4-benzo-[1,3]dioxol-5-yl-1,4-dihydropyridine **3** to the corresponding pyridine derivative **5** (yield 73%). Thorpe–Ziegler cyclization of pyridine **5** proceeded easily to give 3-aminothieno[2,3-*b*]pyridine **6** in 83% yield.

The structures of synthesized compounds were confirmed by spectroscopic methods. In IR spectra, the characteristic absorption band of C≡N group was observed for piperidinium dihydropyridine-2-thiolate **1** at 2182 cm^{-1}, 6-thioxo-1,4,5,6-tetrahydropyridine **2** at 2252 cm^{-1}, 1,4-dihydropyridine **3** at 2193 cm^{-1} and pyridine **5** at 2221 cm^{-1}. Absorption bands of C=O groups of compounds were in agreement with the type of conjugation of C=O groups. In the ^1H NMR spectra, signals characterizing *cis* and *trans* isomers of 6-thioxo-1,4,5,6-tetrahydropyridine **2** were observed. The coupling constant $J_{4,5}$ was 6 Hz for *cis* isomer and 2 Hz for *trans* isomer. The *cis* and *trans* isomers were observed in ratio 4 : 1. In the ^1H NMR spectrum the characteristic signal of 4-H proton of 1,4-dihydropyridine **3** appeared as singlet at 4.37 ppm, but 4-H signal (singlet) of 4,7-dihydrothieno[2,3-*b*]pyridine **4** was shifted downfield to 4.86 ppm.

CONCLUSIONS

Novel benzo[1,3]dioxol-5-yl group containing 4,7-dihydrothieno[2,3-*b*]pyridine **4** and thieno[2,3-*b*]pyridine **6** were obtained by sodium hydroxide-catalyzed Thorpe–Ziegler cyclization of 6-carbamoylmethylsulfanyl-1,4-dihydropyridine **3** and 6-carbamoylmethylsulfanylpyridine **5**. $Mn(OAc)_3$/acetic acid system has been used for oxidation of 1,4-dihydropyridine derivative **3** to pyridine derivative **5**. 6-Carbamoylmethylsulfanyl-1,4-dihydropyridine **3** was prepared by alkylation of piperidinium 1,4-dihydropyridine-6-thiolate **1** with iodoacetamide. Novel 1,4-dihydropyridine-6-thiolate **1** was obtained by three-component condensation of benzo[1,3]dioxol-5-yl-2-cyanothioacrylamide, methyl acetoacetate and piperidine.

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4-BENZO[1,3]DIOKSOL-5-ILTIĒNO[2,3-*b*]PIRIDĪNU SINTĒZE

S. Grīnberga, A. Krauze, L. Krasnova, G. Duburs

K O P S A V I L K U M S

Iegūti benzo[1,3]dioksol-5-ilgrupu saturoši 4,7-dihidrotiēno[2,3-*b*]piridīns **4** un tiēno[2,3-*b*]piridīns **6**, veicot NaOH katalizētu 6-karbamoilmetilsulfanil-1,4-dihidropiridīna **3** un 6-karbamoilmetilsulfanilpiridīna **5** Torpa–Cīglera ciklizēšanu. Lai oksidētu 1,4-dihidropiridīnu **3** līdz piridīnam **5**, izmantots $Mn(OAc)_3$ etiķskābē. 6-Karbamoilmetilsulfanil-1,4-dihidropiridīns **3** iegūts, alkilējot 1,4-dihidropiridīn-2-tiolātu **1** ar jodacetamīdu. Oriģināls 1,4-dihidropiridīn-2-tiolāts **1** iegūts benzo[1,3]dioksol-5-il-2-ciānotioakrilamīda, acetetiķskābes metilestera un piperidīna trīskomponentu reakcijā.

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