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ORIGINAL PAPER

One-pot synthesis of diethyl 4,4′-(1,4-phenylene)bis-[6-(halomethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates] and their bispyrrolocyclization

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Abstract A one-pot synthesis of diethyl 4,4′-(1,4-phenylene)bis[6-(chloromethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates] is proposed via three-component condensation of terephthalic aldehyde, 4-chloroacetoacetic ester, and ureas under Biginelli reaction conditions. Interaction of the obtained precursors that contain two highly reactive binucleophilic groups with primary amines leads to bis-heterocyclization with formation of (1,4-phenylene)-bis(pyrrolo[3,4-*d*]pyrimidine-2,5-diones).

Keywords Biginelli reaction · Bis-heterocyclization · DHPM · Multicomponent reactions

Introduction

Bis-heterocyclization, i.e., successive or simultaneous formation of two analogous heterocycles within one reaction, does not commonly occur in organic synthesis. In the chemistry of the Biginelli reaction, the formation of the initial bis(tetrahydropyrimidines) employing terephthalic aldehyde has only been described in a few papers [1–3]. Low solubility of bis(tetrahydroprimidines) (DHPMs) impedes bringing the halogen atom into the molecule of DHPM, preventing the use of the latter as precursors for further bis-heterocyclization [4, 5]. This fact explains the absence of data on the reactivity, chemical properties, ability to form new heterocyclic systems, regioselectivity, and biological activity of the presented synthons.

The presented work is devoted to the development of simplified synthetic approaches [5, 6] towards reactive initial agents and study of their intramolecular ability to form new heterocyclic systems at their interaction with nucleophiles different in their nature.

Results and discussion

One-pot three-component condensation of methylurea or 1,3-dimethylurea (**1a**–**1b**, Scheme 1), 4-chloroacetoacetic ester (**2**), and terephthalic aldehyde (**3**) at standard Biginelli reaction conditions [7] was performed to synthesize the initial diethyl 4,4′-(1,4-phenylene)bis[6-(halomethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates] (**4a**–**4b**). The implementation of the described heterocondensation allowed us to obtain active precursors **4a**–**4b** that contain two electrophilic groups separated by the phenyl ring.

With the selection of appropriate cyclizing agents, a wide ensemble of different hetaryl 5-, 6-, and 7-membered cyclic systems can be synthesized from two electrophilic *ortho*-groups. During the process of azabisheterocycle construction, our attention was devoted to the formation of five-membered heterocycles. It has been revealed that bis-functionally substituted tetrahydropyrimidines, just as their mono-analogues [4, 5] react with an excess of primary amines (propylamine, monoethanolamine) or aromatic amino acids (*p*-aminobenzoic acid), forming

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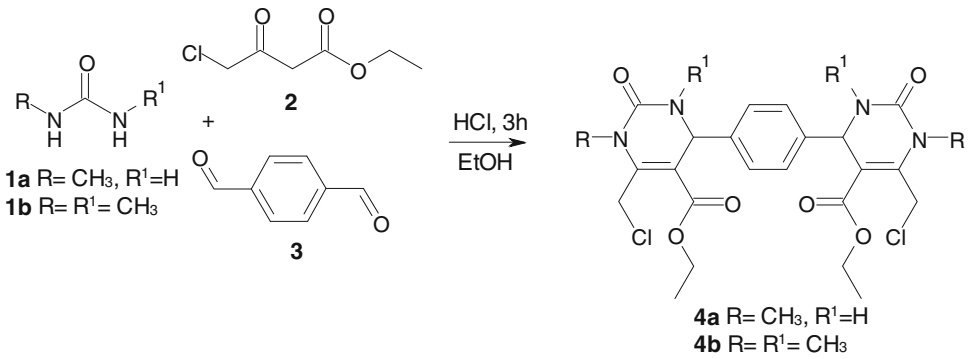
Scheme 1



4,4′-(1,4-phenylene)bis(3,4,6,7-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-diones) (**6a**–**6c**, Scheme 2).

HPLC/MS data revealed that the interaction of the initial compounds with amines at a ratio of 1:1 forms a mixture that consists of three main components—initial bis(chloromethyl-tetrahydropyrimidin-2-one) (**4a**, 64%), monocyclized ethyl 4-(chloromethyl)-6-[4-(2,3,4,5,6,7-hexahydro-1-methyl-2,-5-dioxo-6-propyl-1*H*-pyrrolo[3,4-*d*]pyrimidin-4-yl)phenyl]-1,2,3,6-tetrahydro-3-methyl-2-oxopyrimidine-5-carboxylate (**5**, 25%), and bisdialkylsubstituted tetrahydropyrrolo[3,4-*d*]-pyrimidine (**6a**, 3–5%, Scheme 2). Having employed an excess of a secondary amine (piperidine) in the reaction, bis(6-aminomethyl)-substituted pyrimidines were obtained as a result (**7**, Scheme 2).

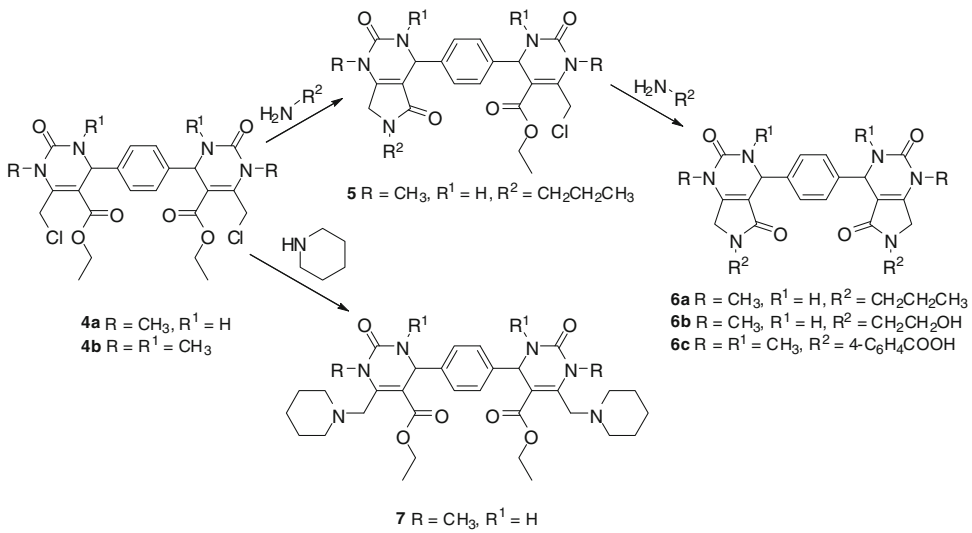
In conclusion, the heterocyclization of bis(6-chloro-methylpyrimidine) derivatives with primary amines proceeds under mild conditions and includes amination at the chloromethyl group followed by a nucleophilic attack on the amino group at the ester fragment with removal of an ethyl alcohol molecule. As a result of this two-stage cyclization, closing of dihydropyrrol-2-one rings takes place, forming tetrahydropyrrolo[3,4-*d*]pyrimidine-2,5-diones.

As a result a simple synthesis approach toward chemically active basic synthons has been developed. It is worth mentioning that the ensemble of the final bis-heterocycles can be significantly widened due to the use of different S-, N-, and O-nucleophilic reagents. The structure and purity of both precursors and final samples were proved by ^{1}H NMR, IR spectroscopy, HPLC/MS, and elemental analyses.

Experimental

All chemicals were obtained from commercial sources and used without any further purification. Melting points were measured on an electrothermal capillary melting point apparatus. IR spectra were recorded with a UR-20 spectrophotometer (KBr platelets). The NMR measurements were carried out on a Varian GEMINI 2000 spectrometer with ^{1}H and ^{13}C frequencies of 400.07 and 100.61 MHz, respectively, at 293 K. ^{1}H NMR spectra were recorded with a spectral width of 8,000 Hz and 32 k data points; ^{13}C NMR spectra were recorded with spectral width of 30,000 Hz and 128 k data points. DMSO-d_6 was used as a solvent and TMS as an internal standard. HPLC/MS was carried out on a system consisting of an Agilent 1100 Series high-pressure liquid chromatograph equipped with a diode matrix and Agilent LC/MSD SL mass-selective detector. HPLC/MS

Scheme 2



parameters: column: Zorbax SB-C18, 1.8 μm, 4.6 × 30 mm; solvents: MeCN–H_2O (95:5), 0.1% TFA; eluent flow: 3 cm^3 min^{-1}; injected sample volume: 1 mm^3; UV detector: $\lambda = 215$, 254, 265 nm; ionization method: chemical ionization under atmospheric pressure; ionization mode: simultaneous scanning of positive and negative ions in *m/z* range 100–650. Elemental analysis was performed on a Perkin-Elmer C, H, N Analyzer, and results were in good agreement (±0.2%) with the calculated values.

Diethyl 4,4′-(1,4-phenylene)bis[6-(chloromethyl)-1,2,3,4-tetrahydro-1-methyl-2-oxopyrimidine-5-carboxylate] (**4a**, $C_{24}H_{28}Cl_2N_4O_6$)

Monomethylurea (**1a**, 10 mmol) was mixed with 1.84 g **2** (11 mmol) and 0.67 g **3** (5 mmol). Three drops of conc. HCl were added to the mixture. The reaction mixture was refluxed for 3 h in 15 cm^3 of EtOH, cooled down and left overnight. The formed yellowish precipitate was separated by filtration and purified by crystallization from 2-PrOH:DMF 3:1. Yellow solid; yield 55%; m.p.: 263 °C (2-PrOH/DMF); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.09$ (d, $^3J = 3.6$ Hz, 2H, 2 × NH), 7.20 (m, 4H, C_6H_4), 5.18 (d, $^2J = 12.0$ Hz, 2H, 2 × CH_2Cl), 5.15 (d, $^3J = 3.6$ Hz, 2H, 2 × NCH), 4.93 (d, $^3J = 12.0$ Hz, 2H, 2 × CH_2Cl), 4.08 (m, 4H, 2 × CH_2CH$_3$), 3.21 (s, 6H, 2 × NCH_3), 1.13 (t, $^3J = 6.8$ Hz, 6H, 2 × CH_2CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 164.35, 152.88, 147.27, 142.35, 126.22, 105.40, 60.26, 51.84, 37.81, 28.92, 13.95 ppm; IR (KBr): $\bar{\nu} = 1{,}630$ (C=C), 1,700, 1,720 (C=O), 3,220 (br, NH) cm^{-1}; HPLC/MS: $m/z = 540$ (M^+).

Diethyl 4,4′-(1,4-phenylene)bis[6-(chloromethyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2-oxopyrimidine-5-carboxylate] (**4b**, $C_{26}H_{32}Cl_2N_4O_6$)

Prepared in analogy to **4a**. Yellow solid; yield 49%, m.p.: 156 °C (2-PrOH/DMF); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.16$ (br.s, 4H, C_6H_4), 5.87 (s, 2H, 2 × NCH), 4.19 (m, 6H, 2 × CH_2CH$_3$), 3.75 (d, $^3J = 12.4$ Hz, 2H, 2 × CH_2Cl), 3.34 (d, $^3J = 12.4$ Hz, 2H, 2 × CH_2Cl), 3.04 (s, 6H, 2 × NCH_3), 2.87 (s, 6H, 2 × NCH_3), 1.19 (t, $^3J = 6.8$ Hz, 6H, 2 × CH_2CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.07$, 151.56, 137.87, 135.33, 126.07, 99.27, 95.37, 61.34, 59.49, 45.93, 35.46, 31.29, 14.00 ppm; IR (KBr): $\bar{\nu} = 1{,}640$ (C=C), 1,670, 1,750 (C=O) cm^{-1}; HPLC/MS: $m/z = 568$ (M^+).

4,4′-(1,4-Phenylene)bis(3,4,6,7-tetrahydro-1-methyl-6-propyl-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione) (**6a**, $C_{26}H_{32}N_6O_4$)

Bis-pyrimidine **4a** (5 mmol) was dissolved in a mixture of 2-PrOH:DMF 3:1. To the solution, an appropriate amine (3 eq, 15 mmol) was added, and the reaction mixture was refluxed for 4 h, cooled down, and left overnight. A white precipitate formed within 12 h. It was separated by filtration, washed with acetone, and purified by crystallization from 2-PrOH:DMF 5:1. White solid; yield 19%; m.p.: 263 °C (2-PrOH/DMF); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.72$ (d, $^3J = 1.2$ Hz, 2H, 2 × NH), 7.25 (br.s, 4H, C_6H_4), 5.15 (s, 2H, 2 × NCH), 4.16 (m, 4H, 2 × NCH_2), 3.19 (m, 4H, $CH_2CH_2CH_3$), 3.00 (s, 6H, 2 × NCH_3), 1.46 (m, 4H, 2 × CH_2CH_3), 0.80 (t, $^3J = 1.2$ Hz, 6H, 2 × CH_2CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 164.25$, 152.72, 147.27, 142.35, 126.24, 105.26, 95.39, 60.27, 51.98, 37.81, 28.86, 13.88 ppm; IR (KBr): $\bar{\nu} = 1{,}610$ (C=C), 1,670 (br, C=O), 3,340 (br, NH) cm^{-1}; HPLC/MS: $m/z = 493$ (M^+).

4,4′-(1,4-Phenylene)bis[3,4,6,7-tetrahydro-6-(2-hydroxyethyl)-1-methyl-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione] (**6b**, $C_{24}H_{28}N_6O_6$)

Prepared in analogy to **6a**. White solid; yield 24%; m.p.: 248 °C (2-PrOH/DMF); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.67$ (br.s, 2H, 2 × NH), 7.28 (s, 4H, C_6H_4), 5.16 (s, 2H, 2 × NCH), 4.64 (t, $^3J = 5.2$ Hz, 2H, 2 × CH_2OH), 4.19 (m, 4H, 2 × NCH_2), 3.46 (m, 4H, 2 × CH_2OH), 3.30 (m, 4H, 2 × CH_2CH_2OH), 3.02 (s, 6H, 2 × CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.08$, 152.04, 151.42, 142.55, 126.12, 103.93, 95.37, 59.59, 52.38, 48.06, 43.96, 29.03 ppm; IR (KBr): $\bar{\nu} = 1{,}650$ (C=C), 1,670, 1,700 (C=O), 3,260–3,430 (br, NH, OH) cm^{-1}; HPLC/MS: $m/z = 497$ (M^+).

4,4′-[4,4′-(1,4-Phenylene)bis(1,2,3,4,5,7-hexahydro-1,3-dimethyl-2,5-dioxo-6H-pyrrolo[3,4-d]pyrimidine-4,6-diyl)]dibenzoic acid (**6c**, $C_{36}H_{32}N_6O_8$)

Prepared in analogy to **6a**. White solid; yield 28%; m.p.: 305 °C (2-PrOH/DMF); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.44$ (br. s, 2H, 2 × COOH), 7.82 (d, $^3J = 8.4$ Hz, 4H, 2 × C_6H_4COOH), 7.74 (d, $^3J = 8.4$ Hz, 4H, 2 × C_6H_4COOH), 7.34 (s, 4H, C_6H_4), 5.34 (s, 2H, 2 × NCH), 4.70 (m, 4H, 2 × CH_2), 3.18 (s, 6H, 2 × 1-CH_3 Pyr), 2.80 (s, 6H, 2 × 3-CH_3 Pyr) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 171.94$, 170.67, 160.19, 157.60, 154.63, 153.81, 152.50, 150.76, 149.07, 133.48, 115.84, 56.78, 55.34, 44.13, 43.81 ppm; IR (KBr): $\bar{\nu} = 1{,}590$ (C=C), 1,690 (C=O), 1,380 (COOH) cm^{-1}; HPLC/MS: $m/z = 662$ (M^+).

Diethyl 4,4′-(1,4-phenylene)bis[1,2,3,4-tetrahydro-1-methyl-2-oxo-6-(piperidin-1-ylmethyl)pyrimidine-5-carboxylate] (**7**, $C_{34}H_{48}N_6O_6$)

Prepared in analogy to **6a**. White solid; yield 18%; m.p.: 216 °C (2-PrOH/DMF); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.59$ (br. s, 2H, 2 × NH), 7.16 (br. s, 4H, C_6H_4), 5.15 (br. s, 2H, 2 × NCH), 4.06 (q, $^3J = 6.4$ Hz, 4H, 2 × CH_2CH$_3$), 3.86 (d, $^2J = 13.2$ Hz, 2H, 2 × CH_2Pip), 3.58 (d, $^2J = 13.2$ Hz, 2H, 2 × CH_2Pip), 3.22 (s, 6H, 2 ×

NCH_3), 2.41 (m, 8H, 2 × Pip-2,6-(CH_2)), 1.42 (m, 12H, 2 × Pip-3,4,5-(CH_2)), 1.13 (t, $^3J = 6.4$ Hz, 6H, 2 × CH_2 CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.00$, 152.61, 148.33, 142.68, 125.89, 105.16, 60.10, 59.59, 53.31, 52.27, 28.75, 25.75, 23.87, 13.98 ppm; IR (KBr): $\bar{\nu} = 1,630$ (C=C), 1,690, 1,710 (C=O), 3,230 (br, NH) cm^{-1}; HPLC/MS: $m/z = 637$ (M^+).

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