Brief Communications

Annulation of a pyridine ring with vicinal ethoxycarbonyl(methyl)pyrimidines

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Pyridoannulation of 5-ethoxycarbonyl-4-methylpyrimidine and 7-methyl-6-ethoxycarbonyl[1,2,4]triazolo[1,5-*a*]pyrimidine derivatives has been studied.

Key words: vicinal ethoxycarbonyl(methyl)pyrimidine, dimethylformamide dimethyl acetal, 4-(2-dimethylaminovinyl)-5-ethoxycarbonylpyrimidines, (*E*)-7-(2-dimethylaminovinyl)-6-ethoxycarbonyl[1,2,4]triazolo[1,5-*a*]pyrimidines, amines, enamines, annulation, pyridopyrimidines.

It has been previously shown that vicinal alkoxycarbonyl(methyl)pyrimidines are convenient precursors for the design of pyridine rings. Thus condensation of 2-substituted 5-methoxycarbonyl-4-methyl-pyrimidines[1] with primary amines and dimethylformamide furnished dihydropyridopyrimidinones (*via* carboxamide intermediates). Cyclization of 2,4-dimethoxy-5-methoxycarbonyl-6-methylpyrimidine with Schiff bases resulted in tetrahydropyridopyrimidines, which were converted to dihydropyridopyrimidinones by treatment with *N*-bromosuccinimide.[2] This approach toward pyrido[4,3-*d*]pyrimidine construction was used for the synthesis of 6-*R*-4-amino-7-hydroxy-2-phenylpyrido[4,3-*d*]pyrimidin-5-ones.[3]

A convenient preparative method for the synthesis of 1,6-naphthyridines has been developed. The procedure involved pyridoannulation of 3,5-diethoxycarbonyl-2,6-dimethylpyridine[4] and 6-ethoxycarbonyl-7-methyl-2-phenylpyrazolopyrimidine derivatives[5] with the use of dimethylformamide dimethyl acetal. In the present work, this method was successfully extended to 2-aminosubstituted pyrimidines (Scheme 1), as well as to fused triazolopyrimidines (Scheme 2).

The first step of pyridoannulation was the reaction of vicinal ethoxycarbonyl(methyl)pyrimidines (**1a—d, 6a—d**) with dimethylformamide dimethyl acetal (**2**). It was found that optimum reaction conditions are refluxing of the reactants in the minimum amount of DMF. The reaction resulted in 4-(2-dimethylaminovinyl)-5-ethoxycarbonyl pyrimidines (**3a—d**) and (*E*)-7-(2-dimethylaminovinyl)-6-ethoxycarbonyl[1,2,4]triazolo[1,5-*a*]pyrimidines **7a—d**. The reaction proceeded more readily in the case of triazolopyrimidines **6a—d** due to high CH-acidity of the methyl group (the triazole moiety effect), and low solubility of the resulting enamines **7a—d**.

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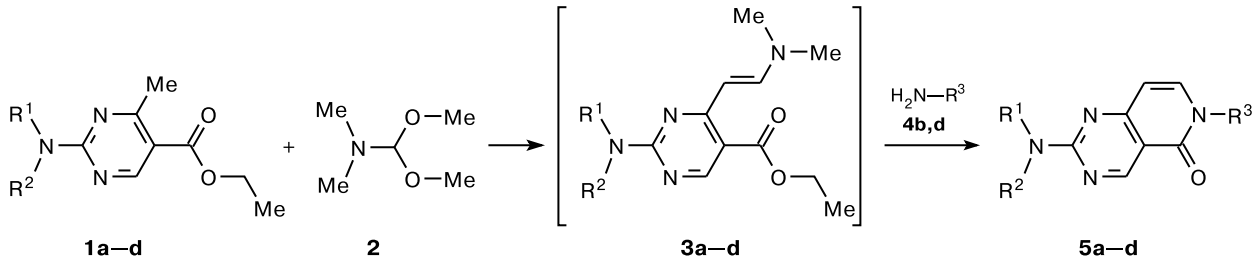
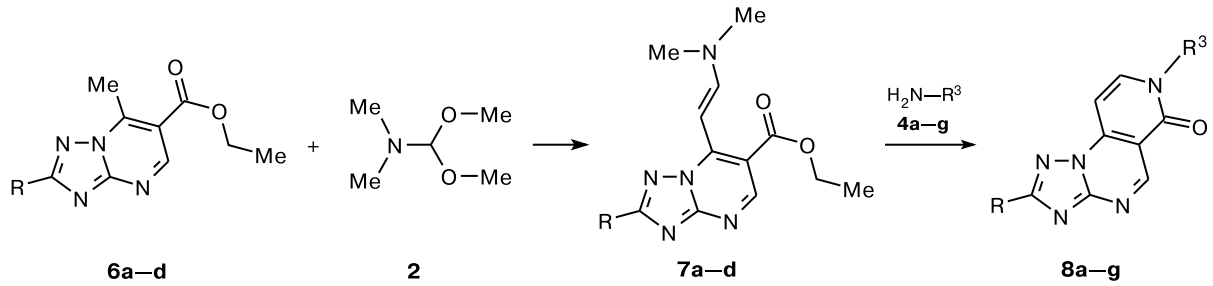
Scheme 1



1a—d **2** **3a—d** **5a—d**

1, 3, 5: $R^1 + R^2 = CH_2—CH_2—O—CH_2—CH_2$ (**a**), $CH_2—CH_2—N(Me)—CH_2—CH_2$ (**b**), $(CH_2)_5$ (**c**), R^1 = Ph, R^2 = H (**d**), $R^3 = CH_2—CH_2$—Ph (**4b, 5a,c**), $CH_2—CH_2—O$—Me (**4d, 5b,d**)

Scheme 2



6a—d **2** **7a—d** **8a—g**

R = H (**6a, 7a, 8a, 8e, 8f**), Me (**6b, 7b, 8b**), CF_3 (**6c, 7c, 8c**), Ph (**6d, 7d, 8d, 8g**)

R^3 = H (**4a, 8a**), $CH_2—CH_2$—Ph (**4b, 8b**), Ph (**4c, 8c**), $CH_2—CH_2—O$—Me (**4d, 8d**), Me (**4e, 8e**), OH (**4f, 8f**), $MeCH_2CHCOOH$ (**4g, 8g**)

The second step involved cyclization of enamines **3a—d**, **7a—d** with a series of primary amines. Isolation and purification of 4-(2-dimethylaminovinyl)-5-ethoxycarbonylpyrimidines **3a—d** was very difficult due to their excellent solubility. Therefore, they were used in cyclization with amines without isolation and characterization. It was found that optimum conditions for the cyclization of (*E*)-7-(2-dimethylaminovinyl)-6-ethoxycarbonyl[1,2,4]-triazolo[1,5-*a*]pyrimidines **7a—d** is refluxing in glacial acetic acid, which being an acceptor of dimethylamine (eliminated in the course of the reaction) shifted the equilibrium toward the product formation. For the synthesis of 7-methyl-6,7-dihydropyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]-pyrimidin-6-one (**8e**) and 7-hydroxy-6,7-dihydropyrido-[3,4-*e*]triazolo[1,2,4][1,5-*a*]pyrimidin-6-one (**8f**), methylamine and hydroxylamine were used as hydrochlorides without hydrogen chloride acceptors. Enamines **7a—d** are yellow crystalline compounds insoluble in hydrocarbons and alcohols and well soluble in chloroform. Pyridopyrimidines **5a—d** and **8a—g** are white solids soluble in DMF and DMSO with heating. The ^{1}H NMR spectra of compounds **5a—d** and **8a—g** exhibited signals for two pyridine protons, which appeared as two doublets (δ 6.18—7.24 and δ 7.59—8.49). The ^{1}H NMR spectra of **8a—g** were devoid of the characteristic signals for the ethoxy and dimethylamino groups present in the spectra of enamines **7a—d**.

The structures of the compounds synthesized were established based on the data from ^{1}H NMR spectroscopy and mass spectrometry and confirmed by elemental analysis data.

Experimental

The course of the reaction as well as the purity of the compounds synthesized was monitored by TLC on precoated silica gel Silufol UV-254 plates. The ^{1}H NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz) relative to Me_4Si (internal standard), DMSO-d_6 was used as a solvent. The mass spectra were run on a LKB 9000 instrument (70 eV).

The starting ethoxycarbonyl(methyl)pyrimidines **1, 6a—d** were synthesized according to the known procedure.[6]

5,6-Dihydropyrido[4,3-*d*]pyrimidin-5-ones 5a—d (general procedure). A mixture of 5-ethoxycarbonyl-4-methylpyrimidine **1a—d** (4 mmol) and dimethylformamide dimethyl acetal **2** (4.3 mmol) in DMF (3 mL) was refluxed for 2—4 h until complete conversion of **1a—d** into enamine **3a—d** (TLC). Then amine **4b,d** was added and refluxing was continued for 3 h. The mixture was cooled, the resulting precipitate was filtered off, washed with Pr^iOH and recrystallized from DMF.

2-Morpholino-6-phenethyl-5,6-dihydropyrido[4,3-*d*]pyrimidin-5-one (5a). Yield 65%, m.p. 145—146 °C. ^{1}H NMR, δ:

2.95 (t, 2 H, CH_2Ph, J = 8 Hz); 3.67 (m, 4 H, CH_2NCH_2 morph., J = 12 Hz); 3.83 (m, 4 H, CH_2OCH_2 morph., J = 12 Hz); 4.10 (t, 2 H, CH_2, J = 8 Hz); 6.18 (d, 1 H, H pyrid., J = 7 Hz); 7.20 (m, 3 H, aryl); 7.28 (m, 2 H, arom.); 7.59 (m, 1 H, H pyrid.); 9.1 (s, 1 H, H pyrimid.). MS, m/z 336 $[M]^+$. Found (%): C, 67.54; H, 5.78; N, 16.80. $C_{19}H_{20}N_4O_2$. Calculated (%): C, 67.84; H, 5.99; N, 16.65.

6-(2-Methoxyethyl)-2-(4-methylpiperazino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-5-one (5b). Yield 77%, m.p. 159—160 °C. ^{1}H NMR, δ: 2.30 (s, 3 H, CH_3); 3.35 (s, 3 H, CH_3O); 3.68 (t, 2 H, CH_2O, J = 8 Hz); 3.82 (m, 4 H, $CH_2N(Me)CH_2$ piperaz.); 3.95 (m, 4 H, CH_2NCH_2 piperaz.); 4.08 (t, 2 H, CH_2, J = 8 Hz); 6.21 (d, 1 H, H pyrid., J = 7 Hz); 7.26 (m, 3 H, arom.); 7.29 (m, 2 H, arom.); 7.60 (m, 1 H, H pyrid.); 9.05 (s, 1 H, H pyrimid.). MS, m/z 303 $[M]^+$. Found (%): C, 59.46; H, 7.00; N, 23.02. $C_{15}H_{21}N_5O_2$. Calculated (%): C, 59.39; H, 6.98; N, 23.09.

6-Phenethyl-2-piperidino-5,6-dihydropyrido[4,3-*d*]pyrimidin-5-one (5c). Yield 65%, m.p. 137—138 °C. ^{1}H NMR, δ: 1.42—1.69 (m, 6 H, $CH_2CH_2CH_2$,.); 2.93 (t, 2 H, CH_2Ph, J = 8 Hz); 3.62 (m, 4 H, CH_2NCH_2 piperid.); 4.09 (t, 2 H, CH_2, J = 7 Hz); 6.14 (d, 1 H, H pyrid., J = 8 Hz); 7.18 (m, 3 H, aryl); 7.25 (m, 2 H, arom.); 7.57 (m, 1 H, H pyrid.); 9.03 (s, 1 H, H pyrimid.). MS, m/z 334 $[M]^+$. Found (%): C, 71.51; H, 6.43; N, 16.88. $C_{20}H_{24}N_4O$. Calculated (%): C, 71.83; H, 6.63; N, 16.75.

2-Anilino-6-(2-methoxyethyl)-5,6-dihydropyrido[4,3-*d*]pyrimidin-5-one (5d). Yield 60%, m.p. 219—221 °C. ^{1}H NMR, δ: 3.34 (s, 3 H, CH_3O); 3.70 (t, 2 H, CH_2O, J = 8 Hz); 4.33 (t, 2 H, CH_2, J = 8 Hz); 7.11 (d, 1 H, H pyrid., J = 7 Hz); 7.36 (m, 3 H, arom.); 7.41 (m, 2 H, arom.); 7.59 (m, 1 H, H pyrid.); 8.12 (s, 1 H, NH); 9.10 (s, 1 H, H pyrimid.). MS, m/z 296 $[M]^+$. Found (%):C, 64.83; H, 5.41; N, 18.94. $C_{16}H_{16}N_4O_2$. Calculated (%): C, 64.85; H, 5.44; N, 18.91.

(*E*)-7-(2-Dimethylaminovinyl)-6-ethoxycarbonyl[1,2,4]triazolo[1,5-*a*]pyrimidines 7a—d (general procedure). A mixture of 6-ethoxycarbonyl-7-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine **6a—d** (5 mmol) and dimethylformamide dimethyl acetal **2** (5.5 mmol) in DMF (5 mL) was refluxed for 20 min. The precipitate that formed was filtered off and recrystallized from DMF.

(*E*)-7-(2-Dimethylaminovinyl)-6-ethoxycarbonyl[1,2,4]triazolo[1,5-*a*]pyrimidine (7a). Yield 95%, m.p. 238—239 °C. ^{1}H NMR, δ: 1.05 (t, 3 H, $CH_2C\underline{H}_3$, J = 8 Hz); 3.05, 3.30 (both s, each 3 H, $N(CH_3)_2$); 3.83 (m, 2 H, $C\underline{H}_2CH_3$); 6.72 (d, 1 H, CH, J = 13 Hz); 8.50 (s, 1 H, pyrimid.); 8.88 (s, 1 H, triaz.); 9.41 (d, 1 H, CH, J =13 Hz). MS, m/z 261 $[M]^+$. Found (%): C, 55.27; H, 5.61; N, 27.25. $C_{12}H_{15}N_5O_2$. Calculated (%): C, 55.16; H, 5.79; N, 26.80.

(*E*)-7-(2-Dimethylaminovinyl)-6-ethoxycarbonyl-2-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine (7b). Yield 85%, m.p. 205—206 °C. ^{1}H NMR, δ: 1.03 (t, 3 H, $CH_2C\underline{H}_3$, J = 8 Hz); 2.06 (s, 3 H, CH_3); 3.02, 3.29 (both s, each 3 H, $N(CH_3)_2$); 3.80 (m, 2 H, $C\underline{H}_2CH_3$); 6.75 (d, 1 H, CH, J = 13 Hz); 8.48 (s, 1 H, pyrimid.); 9.40 (d, 1 H, CH, J =13 Hz). Ms, m/z 275 $[M]^+$. Found (%): C, 56.80; H, 6.17; N, 25.50. $C_{13}H_{17}N_5O_2$. Calculated (%): C, 56.72; H, 6.22; N, 25.44.

(*E*)-7-(2-Dimethylaminovinyl)-6-ethoxycarbonyl-2-trifuoromethyl[1,2,4]triazolo[1,5-*a*]pyrimidine (7c). Yield 90%, m.p. 217—218 °C. ^{1}H NMR, δ: 1.08 (t, 3 H, $CH_2C\underline{H}_3$, J = 8 Hz); 3.05, 3.31 (both s, each 3 H, $N(CH_3)_2$); 3.86 (m, 2 H, $C\underline{H}_2CH_3$); 6.75 (d, 1 H, CH, J =13 Hz); 8.51 (s, 1 H, pyrim.); 9.41 (d, 1 H, CH, J = 13 Hz). MS, m/z 329 $[M]^+$. Found (%): C, 47.49; H, 4.32; N, 21.23. $C_{13}H_{14}F_3N_5O_2$. Calculated (%): C, 47.42; H, 4.29; N, 21.27.

(*E*)-7-(2-Dimethylaminovinyl)-6-ethoxycarbonyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidine (7d). Yield 95%, m.p. 247—248 °C. ^{1}H NMR, δ: 1.07 (t, 3 H, $CH_2C\underline{H}_3$, J = 8 Hz); 3.06, 3.30 (both s, each 3 H, $N(CH_3)_2$); 3.85 (m, 2 H, $C\underline{H}_2CH_3$, J = 8 Hz); 6.82 (d, 1 H, CH, J = 13 Hz); 7.48 (m, 3 H, arom.); 8.29 (m, 2 H, arom.); 8.50 (s, 1 H, H pyrim.); 9.40 (d, 1 H, CH, J = 13 Hz). MS, m/z 337 $[M]^+$. Found (%): C, 64.11; H, 5.65; N, 20.73. $C_{18}H_{19}N_5O_2$. Calculated (%): C, 64.08; H, 5.68; N, 20.76.

6,7-Dihydropyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidin-6-ones 8a—g (general procedure). A mixture of (*E*)-7-(2-dimethylaminovinyl)-6-ethoxycarbonyl[1,2,4]triazolo[1,5-*a*]-pyrimidine **7a—d** (4 mmol) and amine **4a—g** (4 mmol) in glacial acetic acid (5 mL) was refluxed for 30 min. The reaction mixture was cooled, the resulting precipitate was filtered off and washed with water to give compounds **8a—g.**

6,7-Dihydropyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidin-6-one (8a). Yield 75%, m.p. 251—253 °C. ^{1}H NMR, δ: 7.05 (d, 1 H, H pyrid., J = 7 Hz); 8.02 (d, 1 H, H pyrid., J = 7 Hz); 8.75 (s, 1 H, H triaz.); 9.30 (s, 1 H, H pyrimid.); 12.40 (br.s, 1 H, NH). MS, m/z 187 $[M]^+$. Found (%): C, 51.40; H, 2.66; N, 37.43. $C_8H_5N_5O$. Calculated (%): C, 51.34; H, 2.69; N, 37.42.

2-Methyl-7-phenethyl-6,7-dihydropyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidin-6-one (8b). Yield 85%, m.p. 241—242 °C. ^{1}H NMR, δ: 2.05 (s, 3 H, CH_3); 3.04 (t, 2 H, CH_2Ph, J = 8 Hz); 4.28 (t, 2 H, CH_2, J = 8 Hz); 7.03 (d, 1 H, H pyrid., J = 7 Hz); 7.21—7,32 (m, 5 H, arom.); 8.15 (d, 1 H, H pyrid., J = 7 Hz); 9.33 (s, 1 H, H pyrimid.). MS, m/z 305 $[M]^+$. Found (%): C, 66.45; H, 4.75; N, 23.02. $C_{16}H_{13}N_5O$. Calculated (%): C, 66.87; H, 4.95; N, 22.94.

7-Phenyl-2-trifluoromethyl-6,7-dihydropyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidin-6-one (8c). Yield 88%, m.p. 257—259 °C. ^{1}H NMR, δ: 7.12 (d, 1 H, H pyrid., J = 7 Hz); 7.50—7.62 (m, 5 H, arom.); 8.30 (d, 1 H, H pyrid., J = 7 Hz); 9.35 (s, 1 H, H pyrimid.). MS, m/z 331 $[M]^+$. Found (%): C, 54.43; H, 2.41; N, 21.16. $C_{15}H_8F_3N_5O$. Calculated (%): C, 54.39; H, 2.43; N, 21.14.

7-(2-Methoxyethyl)-2-phenyl-6,7-dihydropyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidin-6-one (8d). Yield 91%, m.p. 211—212 °C. ^{1}H NMR, δ: 3.28 (s, 3 H, CH_3O), 3.65 (t, 2 H, CH_2O, J = 8 Hz); 4.25 (t, 2 H, CH_2, J = 8 Hz); 7.15 (d, 1 H, H pyrid., J = 7 Hz); 7.50 (m, 3 H, arom.); 8.11 (d, 1 H, H pyrid., J = 7 Hz); 8.30 (m, 2 H, arom.); 9.44 (s, 1 H, H pyrimid.). MS, m/z 321 $[M]^+$. Found (%): C, 63.59; H, 4.68; N, 21.73. $C_{17}H_{15}N_5O_2$. Calculated (%): C, 63.54; H, 4.71; N, 21.79.

7-Methyl-6,7-dihydropyrido[3,4-*e*]triazolo[1,2,4][1,5-*a*]pyrimidin-6-one (8e). Yield 79%, m.p. 236—237 °C. ^{1}H NMR, δ: 3.60 (s, 3 H, CH_3); 7.07 (d, 1 H, H pyrid., J = 7 Hz); 8.30 (d, 1 H, H pyrid., J = 7 Hz); 8.73 (s, 1 H, H triaz.); 9.43 (s, 1 H, H pyrimid.). MS, m/z 201 $[M]^+$. Found (%): C, 53.67; H, 3.52; N, 34.78. $C_9H_7N_5O$. Calculated (%): C, 53.73; H, 3.51; N, 34.81.

7-Hydroxy-6,7-dihydropyrido[3,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidin-6-one (8f). Yield 63%, m.p. >260 °C (infl.). ^{1}H NMR, δ: 7.05 (d, 1 H, H pyrid., J = 7 Hz); 8.49 (d, 1 H, H pyrid., J = 7 Hz); 8.75 (s, 1 H, H triaz.); 9.48 (s, 1 H, H pyrimid.); 12.28 (br.s, 1 H, OH). MS, m/z 203 $[M]^+$. Found (%): C, 47.25; H, 2.46; N, 34.43. $C_8H_5N_5O_2$. Calculated (%): C, 47.30; H, 2.48; N, 34.47.

2-(6-Oxo-2-phenyl-6,7-dihydropyrido[3,4-*e*][1,2,4]triazolo-[1,5-*a*]pyrimidin-7-yl)butyric acid (8g). Yield 86%, m.p. 265—267 °C. ^{1}H NMR, δ: 0.88 (m, 3 H, CH_3); 2.05—2.30 (m, 2 H, CH_2); 5.30 (m, 1 H, CH); 7.24 (d, 1 H, H pyrid., J = 7 Hz); 7.55 (m, 3 H, arom.); 8.24 (m, 2 H, arom.); 8.30 (d, 1 H, H pyrid., J = 7 Hz); 9.32 (s, 1 H, H pyrimid.); 13.25 (br.s, 1 H, COOH). MS, m/z 273 $[M]^+$. Found (%): C, 52.82; H, 4.03; N, 25.67. $C_{12}H_{11}N_5O_3$. Calculated (%): C, 52.75; H, 4.06; N, 25.63.

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