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Synthesis of Some New Pyridines, Thienopyridines and Pyrido[2,3:4',5']thieno[3',2'-*d*]pyrimidin-8-ones from 2-acetylbenzoimidazole

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Reaction of 2-acetylbenzoimidazole **1** with some arylaldehydes under different conditions gave chalcones, 1,5-pentanediones and pyridines. Treatment of chalcones with various types of reagents gave the corresponding new pyridines, thienopyridines, pyrido[2,3:4',5']thieno[3',2'-*d*]-pyrimidin-8-ones *via* initial addition of active methylene or amino group to the double bond followed by cyclization.

INTRODUCTION

Benzoimidazole derivatives have been found to possess various biological activities.[1–3] We have recently started a program of the synthesis of heterocyclic compounds including pyridine and thienopyridine derivatives.[4,5] Within our ongoing program, we intend to extend the existing synthetic route using 2-acetylbenzoimidazol **1** as the key compound in the synthesis of some new heterocycles with potential biological activity.

RESULTS AND DISCUSSION

The key precursor 2-acetylbenzoimidazole **1**[6] was reacted with arylaldehydes to afford chalcone analogues **2**.[7,8] Treatment of **2** with equimolar amounts of 2-amino-2-methyl-acrilonitrile in refluxing glacial acetic acid afforded the corresponding 4-aryl-6-(1*H*-benzoimidazol-2-yl)-2-methyl-1,4-dihydropyridine-3-carbonitrile **(3a–c)** in acceptable yields, Scheme 1. Structure of compounds **3a–c** was elucidated by analytical and spectroscopic data. Thus, the IR (KBr) spectra of **3a** showed broad absorption bands at 3386–3332 (NH) and 2221 cm^{-1} (C≡N) and its ^1H NMR spectrum showed a doublet signal at δ = 4.6 ppm (1H) attributed to H-4 pyridine, besides other expected signals. Also, its mass spectrum revealed a molecular ion peak at *m/z* = 342 (23 %) corresponding to the molecular formula $C_{21}H_{18}N_4O$. Alternatively, refluxing of equimolar amounts of each **2a–d** and cyanothioacetamide in ethanol, in the presence of a catalytic amount of piperidine, afforded 4-aryl-6-(benzoimidazol-2-yl)-2-mercapto-pyridine-3-carbonitrile **7a–d.** Compound **7** is assumed to be formed *via* initial Michael adduct **4** followed by intramolecular cyclodehydration and spontaneous autoxidation under the reaction conditions.[9,10] Although cyclization

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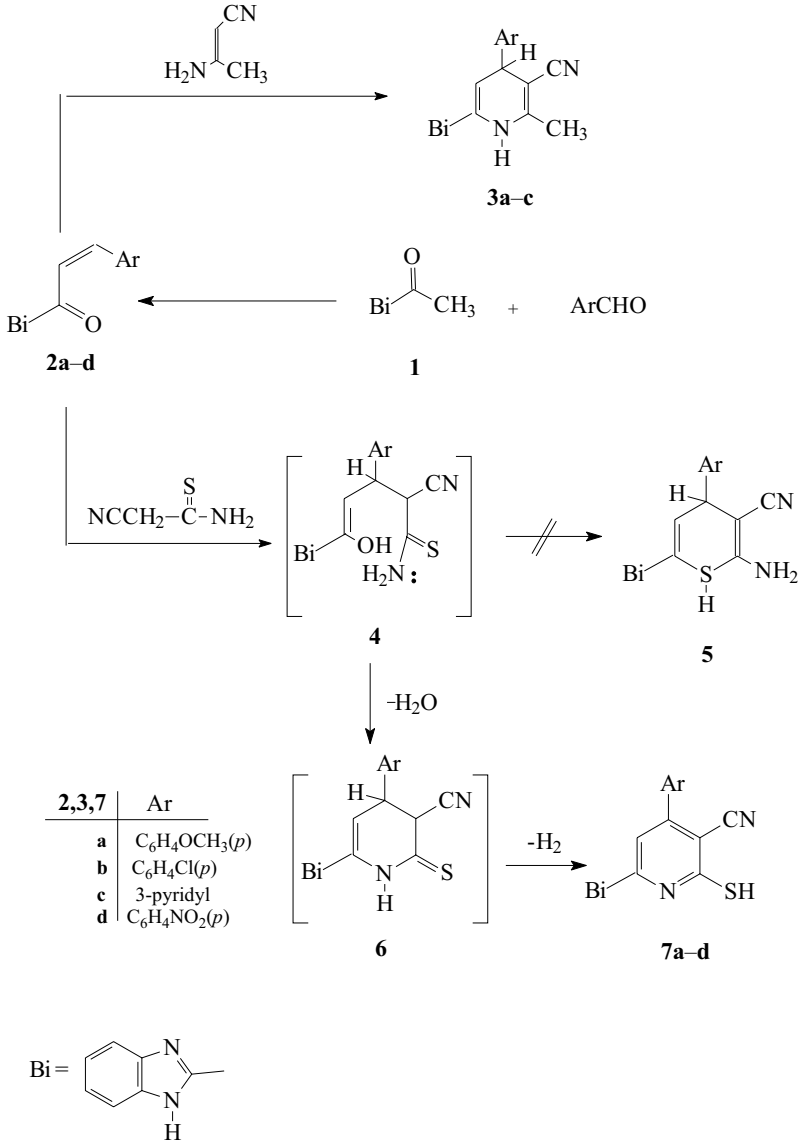


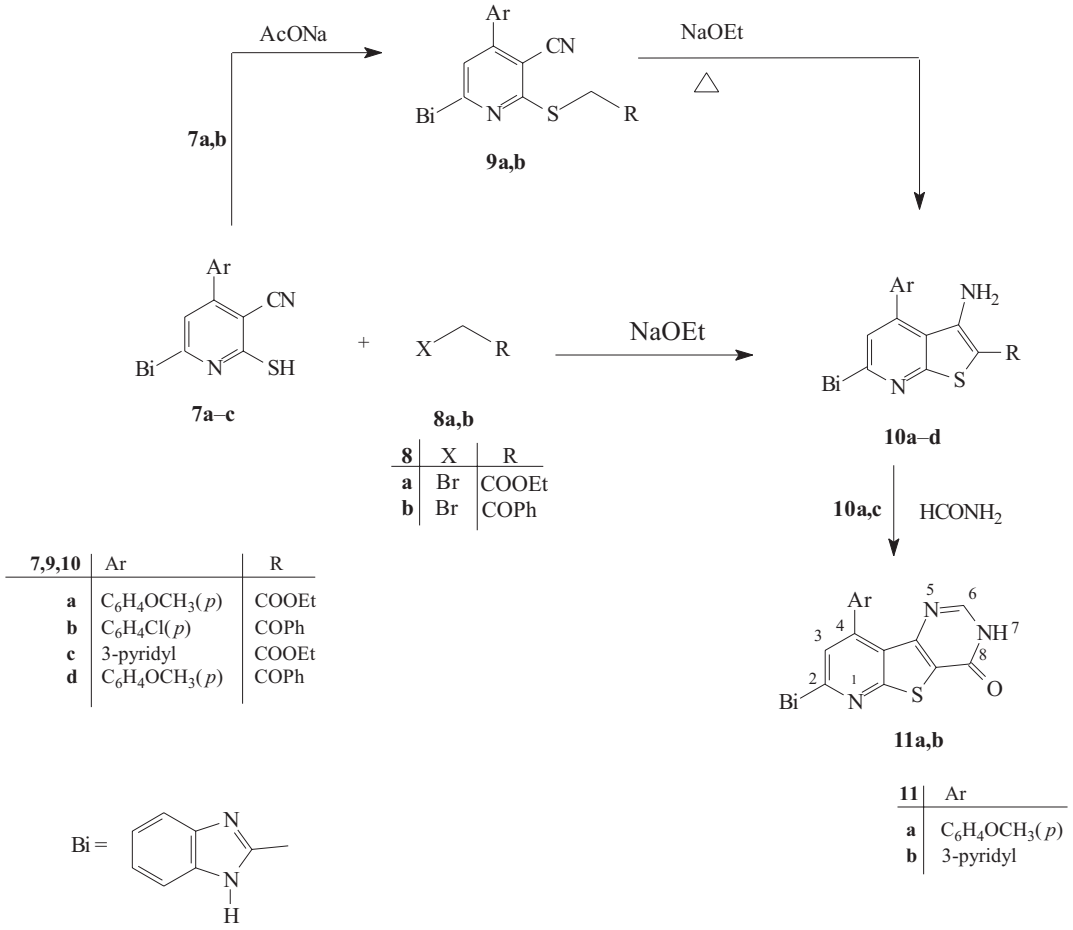
Scheme 1. Preparation of **3** and intermediate **7**.

of **4** to 2-aminothiopyran derivative **5** is also possible, we did not observe formation of this product. The structure of **7** was assigned to the isolated products **7a–d** on the basis of elemental analysis, IR and in particular ^{1}H NMR spectra; the latter revealed the absence of H-4 in the thiopyran unit.

An approach starting from **7a–c** the synthesis of 3-amino-4-aryl-6-(1*H*-benzoimidazol-2-yl)thieno[2,3-*b*]-pyridines **10a–d** through their condensation with active halomethylene compounds **8a,b**, in boiling ethanol in the presence of sodium ethoxide, was studied, Scheme 2. This reaction presumably occurred through intermediate **9**, which was obtained when the less basic catalyst sodium acetate was used. The structure of compounds **10a–d** was confirmed on the basis of their correct elemental analyses as well as compatible spectral data. Condensation of compounds **10a,c** with formamide afforded 4-aryl-2-(1*H*-benzoimidazol-2-yl)-7*H*-pyrido[2,3:4',5']thieno[3,2-*d*]pyrimidin-8-one **11a,b**, respectively. The structure of compounds **11a,b** was elucidated by analytical and spectroscopic data. Thus, the IR spectra of **11a,b** revealed the absence of (NH_2) function, and showed absorption bands at 3440 (NH) and 1705–1689 cm^{-1} (CO). The mass spectrum of **11b** showed the molecular ion peak *m/z* = 396 (23 %) corresponding to the molecular formula $C_{21}H_{12}N_6OS$.

The reaction of heterocyclic amines and aromatic α,β-unsaturated ketones is a very convenient and versatile method for fusion of a pyridine ring in polycyclic heterocycles.[13,14] Nucleophilic amines **12a,b** can attack the carbonyl carbon atom C1 or C3 of the ketones **2**. Actually, only the first attack takes places and the corresponding **14a–e** or **17a,b** were isolated.

Reaction of equimolar amounts of a mixture of **2** and **12** in DMF for 6–8 hours gave pyrido[2,3-*d*]pyrimi-



8	X	R
a	Br	COOEt
b	Br	COPh

7,9,10	Ar	R
a	$C_6H_4OCH_3(p)$	COOEt
b	$C_6H_4Cl(p)$	COPh
c	3-pyridyl	COOEt
d	$C_6H_4OCH_3(p)$	COPh

11	Ar
a	$C_6H_4OCH_3(p)$
b	3-pyridyl

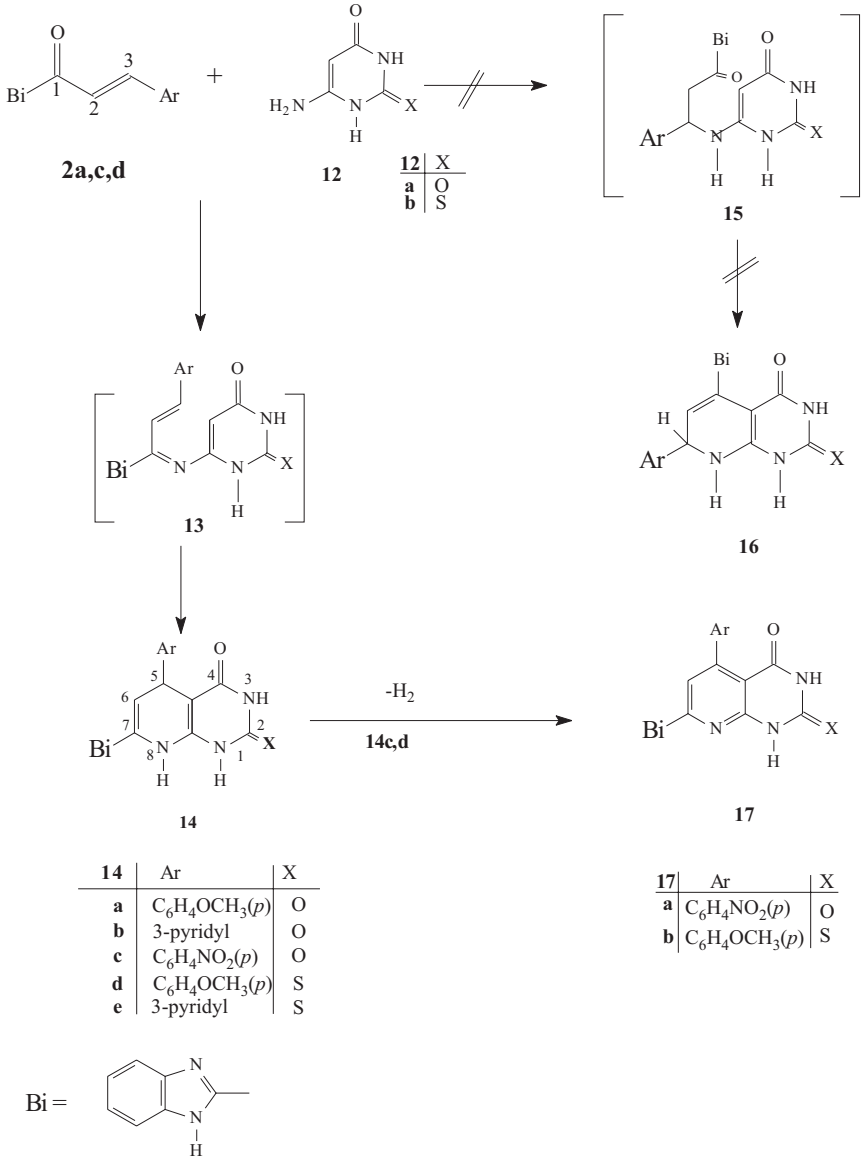
Scheme 2. Formation of **10** and **11**.

dines **14a–e**. These compounds and their oxo and thioxo derivatives reveal interesting biological and physiological properties.[11,12] The structure of **14a–e** was deduced from their analytical and spectral data. Thus, their IR spectra showed absorption bands at 3433–3180 (NH), 1720–1687 cm^{-1} (amide CO). The ^1H NMR (DMSO-d_6) spectrum of **14b** showed, in addition to the expected signals, two doublets at δ = 4.76 and 5.93 ppm assigned to H-5 and H-6, respectively, three sharp singlets at δ of 10.21, 10.66 and 11.41 ppm corresponding to H-8, H-1 and H-3, respectively. Also, the mass spectrum of **14b** showed the molecular ion peak at *m/z* = 358 (100 %), corresponding to the molecular formula $C_{19}H_{14}N_6O_2$. On the other hand, prolonged reaction time to over 20 hours gave **17a,b**; the conversion was controlled by TLC. The ^1H NMR (DMSO-d_6) of **17a** revealed, in addition to the expected signals, singlets at δ = 7.26, 11.44 and 11.83 ppm due to H-6, H-1 and H-3, respectively, and disappearance of H-5 and H-8 signals at 4.76 and 10.21 ppm, respectively, Scheme 3.

Finally, on heating **1** with arylaldehydes **18a–c** in the 2:1 mole ratio in the presence of NH_4OAc,[15] 4-aryl-2,6-bis(benzoimidazol-2-yl)pyridine **(20a–c)** were isolated in good yield. The structure of these symmetric compounds was elucidated from the IR spectra showing absorption bands at 3425–3255 cm^{-1} (NH); the ^{1} H NMR (DMSO-d_6) spectrum of **20b** showed, in addition to the expected signals, a singlet at δ = 3.91 ppm assigned to OCH_3. Also, the mass spectrum of **20b** showed the molecular ion peak *m/z* = 417 (100 %) corresponding to the molecular formula $C_{26}H_{19}N_5O$. Reaction of **1** with arylaldehydes **18b,c** in a 2:1 mole ratio in aqueous ethanolic NaOH solution afforded the intermediary acyclic 3-aryl-1,5-bis(benzoimidazol-2-yl)pentan-1,5-diones **19a,b** which underwent a facile ring closure in the presence of NH_4OAc to give products **20b,c**, Scheme 4.

EXPERIMENTAL

Melting points were uncorrected, determined in glass capillary tubes on a MEL-TEMP II melting point apparatus. Infrared spectra were recorded with a Shimadzu FTR-8201 PC spectrophotometer. ^1H NMR were obtained on a Varian Gemini (200 MHz) spectrometer using DMSO-d_6 and/or $CDCl_3$-d_1 as solvent and TMS as internal reference. Mass spectra were performed on a Shimadzu GCMS -QP 1000EX spectrometer using a direct inlet system and EI-QI MS LRUPL. Microanalysis was performed by the Microanalytical Unit at the Cairo University. Thin layer chromatogra-



Scheme 3. Routes to pyrido[2,3–*d*]pyrimidines **17**.

phy was carried out on 5×20 cm plates coated with silica gel GF 254 type 60, mesh size 50–250. Compounds **1**[8] and **2**[9,10] were prepared according to the reported method.

*4-Aryl-6-(1*H*-benzoimidazol-2-yl)-2-methyl-1,4-dihydropyridine-3-carbonitrile **(3a–c)***

General Procedure. – To a solution of compound **2** (1.0 mmol) in acetic acid (10 mL), 2-amino-2-methyl acrylonitrile (1.0 mmol) was added. The reaction mixture was heated under reflux for 6 hours. After cooling, the solid obtained was collected by filtration and recrystallized from ethanol.

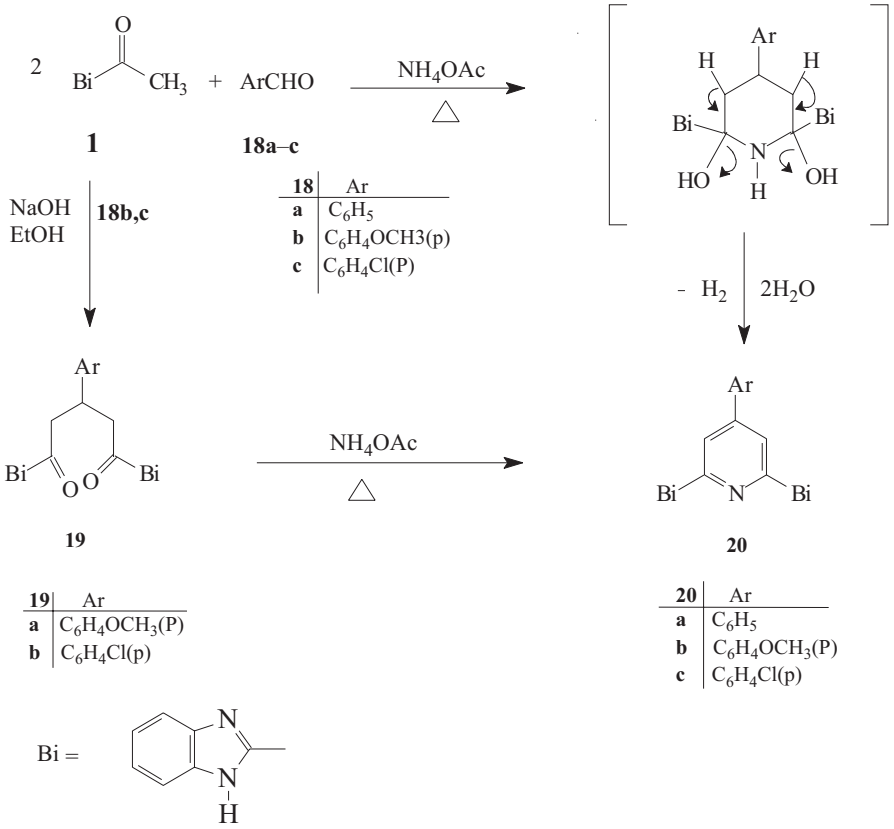
*6-(1*H*-Benzoimidazol-2-yl)-2-methyl-4-(4-methoxyphenyl)-*1,4-*dihydropyridine-3-carbonitrile* **(3a)**. – Obtained from **2a** as pale yellow crystals from ethanol, 0.246 g (73 %); m.p. 231 °C; IR(KBr) ν_{max}/cm^{-1}: 3386 (NH), 2221 (C≡N); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 2.5 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.6 (d, J = 6.2 Hz, 1H, H-4 pyridine), 7.21–7.93 (m, 9H, Ar-H, H-5 pyridine), 8.22 (s,1H, NH) and 8.94 (s,1H, NH pyridine); MS *m/z:* 342 (M$^+$, 23 %).

Anal. Calcd. for $C_{21}H_{18}N_4O$ (M_r = 342.63): C 73.62, H 5.29, N 16.42 %; found: C 73.70, H 5.00, N 16.20 %.

*6-(1*H*-Benzoimidazol-2-yl)-4-(4-chlorophenyl)-2-methyl-*1,4-*dihydropyridine-3-carbonitrile* **(3b)**. – Obtained from **2b** as yellow crystals from ethanol, 0.234 g (68 %), m.p. 239 °C; IR (KBr) ν_{max}/cm^{-1}: 3332 (NH), 2221 (C≡N). ^{1}H NMR (DMSO-d$_6$) δ/ppm: 2.2 (s, 3H, CH_3), 4.6 (d, 1H, J = 6.2 Hz, H-4 pyridine), 7.18–7.96 (m, 9H, Ar-H, H-5 pyridine), 8.15 (s, 1H, NH) and 9.10 (s, 1H, NH pyridine).

Anal. Calcd. for $C_{20}H_{15}N_4Cl$ (M_r = 347.09): C 69.21, H 4.35, N 16.21 %; found: C 69.30, H 4.10, N 16.10 %.

*6-(1*H*-Benzoimidazol-2-yl)-2-methyl-4-(4-nitrophenyl)-*1,4-*dihydropyridine-3-carbonitrile* **(3c)**. – Obtained from **2d** as deep yellow crystals from ethanol, 0.25 g (71 %), m.p.



Scheme 4. Synthesis of pyridine derivatives 20.

254 °C; IR (KBr) ν_{max}/cm^{-1}: 3349 (NH), 2200 (C≡N); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 2.31 (s, 3H, CH$_3$), 4.61 (d, 1H, J = 6.2 Hz, H-4 pyridine), 7.21–8.14 (m, 9H, Ar-H, H-5 pyridine), 8.31 (s, 1H, NH) and 9.12 (s, 1H, NH pyridine).

Anal. Calcd. for $C_{20}H_{15}N_5O_2$ (M_r = 357.66): C 67.17, H 4.22, N 19.66 %; found: C 67.10, H 4.00, N 19.50 %.

*Preparation of **7a–d***

General Procedure. – To a solution of **2** (5.0 mmol) in ethanol (30 mL) containing a few drops of piperidine, cyanothioacetamide (5.0 mmol) was added. The mixture was heated under reflux for 6 hours and cooled; the precipitate formed was filtered off and recrystallized from a proper solvent**.**

*6-(1*H*-Benzoimidazol-2-yl)-2-mercapto-4-(4-methoxyphenyl)-1,4-dihydropyridine-3-carbonitrile **(7a)***. – Obtained from **2a** as yellow crystals (from benzene-methanol), 1.3 g (73 %), m.p. 317 °C; IR(KBr) ν_{max}/cm^{-1}: 3340 (NH), 2228 (C≡N), 1287 (C=S); ^{1} H NMR (DMSO-d$_6$) δ/ppm: 3.88 (s, 3H, OCH$_3$), 7.16–7.8 (m, 8H, Ar-H), 8.21(s, 1H, H-5 pyridine), 8.42 (s, 1H, NH) and 9.31(s, 1H, NH pyridine), MS *m/z*: 358 (M$^+$, 91 %).

Anal. Calcd. for $C_{20}H_{14}N_4OS$ (M_r = 358.59): C 66.99, H 3.93, N 15.69 %; found: C 66.80, H 3.70, N 15.60 %.

*6-(1*H*-Benzoimidazol-2-yl)-2-mercapto-4-(4-chlorophenyl)-1,4-dihydropyridine-3-carbonitrile **(7b)***. – Obtained from **2b**, 1.3 g (72 %), as pale yellow crystals from ethanol, m.p. 280 °C; IR(KBr) ν_{max}/cm^{-1}: 3456 (NH), 2237 (C≡N), 1267 (C=S); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 7.13–7.81 (m, 8H, Ar-H), 8.01(s, 1H, H-5 pyridine), 8.44 (s, 1H, NH) and 9.30 (s, 1H, NH pyridine).

Anal. Calcd. for $C_{19}H_{11}N_4SCl$ (M_r = 363.16): C 62.86, H 3.05, N 15.50 %; found: C 62.70, H 2.90, N 15.30 %.

*6-(1*H*-Benzoimidazol-2-yl)-2-mercapto-4-(3-pyridyl)-1,4-dihydropyridine-3-carbonitrile **(7c)***. – Obtained from **2c** as yellow crystals from ethanol, 1.13 g (69 %), m.p. 253 °C; IR(KBr) ν_{max}/cm^{-1}: 3335(NH), 2214 (C≡N), 1285 (C=S); MS *m/z*: 330 (M$^+$**,** 35 %).

Anal. Calcd. for $C_{18}H_{11}N_5S$ (M_r = 329.62): C 65.59, H 3.36, N 21.34; found: C 65.50, H 3.30, N 21.10 %.

*6-(1*H*-Benzoimidazol-2-yl)-2-mercapto-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carbonitrile **(7d)***. – Obtained from **2d** as yellow crystals from methanol, 1.3 g (70 %), m.p. 263 °C; IR(KBr) ν_{max}/cm^{-1}: 3390 (NH), 2221 (C≡N), 1249 (C=S); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 7.34–8.01 (m, 8H, Ar-H), 8.21 (s, 1H, H-5 pyridine), 8.2 (s, 1H, NH) and 9.10 (s, 1H, NH pyridine); MS *m/z*: 373 (M$^+$, 12 %).

Anal. Calcd. for $C_{19}H_{11}N_5O_2S$ (M_r = 373.62): C 61.08, H 2.96, N 18.82 %; found: C 60.80, H 2.90, N 18.60 %.

*4-Aryl-[6-(1*H*-benzoimidazol-2-yl)-3-cyanopyridin-2-sulfanyl] derivatives **(9a–b)***

General Procedure. – Compound **7a,c** (2.0 mmol) was dissolved in ethanolic solution of sodium acetate (20 mL, 20 %).

Then the appropriate alkylating agent **8a,b** (2.0 mmol) was added and the mixture was heated under reflux for 30 min. After cooling, the mixture was poured onto cold water (80 mL), the precipitate was collected by filtration and recrystallized from a proper solvent.

*[6-(1*H*-Benzoimidazol-2-yl)-3-cyano-4-(4-methoxyphenyl)pyridin-2-yl-sulfanyl]acetic acid ethyl ester* ***(9a)***. – Obtained from **7a** and ethylbromoacetate as pale yellow crystals from benzene; 0.70 g (79 %), m.p. 255 °C; IR(KBr) ν_{max}/cm^{-1}: 3355 (NH), 2221(C≡N), 1720 (CO-ester); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.2 (t, 3H, J = 7 Hz, CH_3), 3.89 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2), 4.23 (q, 2H, J = 7 Hz, CH_2), 7.23–7.5 (m, 9H, Ar-H), and 8.2 (s, 1H, NH); MS *m/z*: 444 (M^+, 100 %).

Anal. Calcd. for $C_{24}H_{20}N_4O_3S$ (M_r = 444.66): C 64.83, H 4.53, N 12.65 %; found: C 64.60, H 4.50, N 12.50 %.

*[6-(1*H*-Benzoimidazol-2-yl)-3-cyano-4-(4-chlorophenyl)pyridin-2-yl-sulfanyl] phenylethanone* ***(9b)***. – Obtained from **7b** and phenacyl bromide as yellow crystals from benzene; 0.71 g (74 %); m.p. 229 °C; IR(KBr) ν_{max}/cm^{-1}: 3355 (NH), 2216 (C≡N), 1705 (CO); ^{1}H NMR ($CDCl_3$) δ/ppm: 4.50 (s, 2H, CH_2), 7.24–7.89 (m, 13H, Ar-H), 8.14 (s,1H, H-5 pyridine) and 8.30 (s, 1H, NH).

Anal. Calcd. for $C_{27}H_{17}N_4OClS$ (M_r = 481.19): C 67.39, H 3.55, N 11.69 %; found: C 67.20, H 3.50, N11.50 %.

Preparation of ***10a–d***

To compound **7** (2.0 mmol) in ethanolic sodium ethoxide solution (25 ml EtOH, 0.1 g Na), an alkylating agent (2.0 mmol) was added. The reaction mixture was heated under reflux for 4 hours. After cooling, the mixture was poured onto cold water (75 mL) and the solid product was filtered and recrystallized from benzene.

*3-Amino-6-(1*H*-benzoimidazol-2-yl)-4-(4-methoxyphenyl)-thieno[2,3-*b*]pyridine-2-carboxylic acid ethyl ester* ***(10a)***. – Obtained from **7a** and ethylbromoacetate as yellow crystals; 0.65 g (74 %); m.p. 241 °C; IR(KBr) ν_{max}/cm^{-1} : 1717 (CO), 3355–3410 (NH_2); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.45 (t, 3H, J = 3 Hz, CH_3), 3.91 (s, 3H, OCH_3), 4.44 (q, 2H, J = 3 Hz, CH_2), 5.89 (s, 2H, NH_2), 7.24–7.98 (m, 9H, Ar-H, H-5 pyridine) and 8.24 (s, 1H, NH); MS m/z: 444 (M^+, 100 %).

Anal. Calcd. for $C_{24}H_{20}N_4O_3S$ (M_r = 444.66): C 64.83, H 4.53, N 12.65 %; found : C 64.80, H 4.50, N 12.40 %.

*3-Amino-6-(1*H*-benzoimidazol-2-yl)-4-(4-chlorophenyl)thieno[2,3-*b*]pyridine-2-phenylmethanone* ***(10b)***. – Obtained from **7b** and phenacylbromide as yellow crystals; 0.6 g (62 %); m.p. 285 °C; IR(KBr) ν_{max}/cm^{-1}: 3390–3483 (NH_2), 1690 (CO); ^{1}H NMR ($CDCl_3$) δ/ppm: 5.92 (s, 2H, NH_2), 7.32–8.1 (m, 14H, Ar-H, H-5 pyridine), 8.31(s, 1H, NH).

Anal. Calcd. for $C_{27}H_{17}N_4OClS$ (M_r = 481.19): C 67.39, H 3.55, N 11.69 %; found: C 67.30, H 3.40, N 11.60 %.

*3-Amino-6-(1*H*-benzoimidazol-2-yl)-4-(3-pyridyl)thieno[2,3-*b*]pyridine-2-carboxylic acid ethyl ester* ***(10c)***. – Obtained from **7c** and ethylbromoactate as brown crystals; 0.54 g (66 %); m.p. 271 °C; IR(KBr) ν_{max}/cm^{-1}: 3463–3332 (NH_2), 1712 (CO); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.21(t, 3H, J = 3 Hz, CH_3), 4.21(q, 2H, J = 3 Hz, CH_2), 5.91 (s, 2H, NH_2), 7.45–8.10 (m, 9H, Ar-H, H-pyridine), 8.51(s, 1H, NH); MS m/z: 415 (M^+, 36 %).

Anal. Calcd. for $C_{22}H_{17}N_5O_2S$ (M_r = 415.69): C 63.57, H 4.12, N 16.92 %; found: C 63.50, H 4.00, N 16.70 %.

*3-Amino-6-(1*H*-benzoimidazol-2-yl)-4-(4-methoxyphenyl)thieno[2,3-*b*]pyrdine-2-phenyl methanone* ***(10d)***. – Obtained from **7a** and phenacylbromide as yellow crystals from benzene, 0.66 g (70 %); m.p. 173 °C, IR(KBr) ν_{max}/cm^{-1}: 3320–3473 (NH_2), 1700 (CO); ^{1}H NMR ($CDCl_3$) δ/ppm: 3.93 (s, 3H, OCH_3), 5.82 (s, 2H, NH_2), 7.26–7.9 (m, 14H, Ar-H, H-5 pyridine), 8.27 (s, 1H, NH); MS m/z: 476 (M^+, 100 %).

Anal. Calcd. for $C_{28}H_{20}N_4O_2S$ (M_r = 476.72): C 70.55, H 4.22, N 11.80 %; found : C 70.40, H 4.10, N 11.70 %.

*4-Aryl-2-(1*H*-benzoimidazol-2-yl)-7*H*-pyrido[2,3:4',5']-thieno[3',2'-*d*]pyrimidin-8-one* ***(11a,b)***

General Procedure. – Compound **10a,c** (1.0 mmol) in formamide (10 mL) was heated under reflux for 6 h. The mixture was cooled, diluted with water (40 mL) and the resulting precipitate was collected and recrystallized from DMF.

*2-(1*H*-Benzoimidazol-2-yl)-4-(4-methoxyphenyl)-7*H*-pyrido-[2,3:4',5']thieno[3',2'-*d*]pyrimidin-8-one* ***(11a)***. – Obtained from **10a** as yellowish-brown crystals, 0.29 g (68 %) m.p. 215 °C; IR(KBr) ν_{max}/cm^{-1}: 3440 (NH), 1689 CO), ^{1}H NMR (DMSO-d_6) δ/ppm: 3.56 (s, 3H, OCH_3), 7.25–7.90 (m, 9H, Ar-H, H-3 pyridine), 8.51 (s, 1H, NH), 8.91 (s,1H, H-6 pyrimidine), 9.51(s, 1H, NH).

Anal. Calcd. for $C_{23}H_{15}N_5O_2S$ (M_r = 425.69): C 64.89, H 3.54, N 16.52 %; found: C 64.70, H 3.40, N 16.30 %.

*2-(1*H*-Benzoimidazol-2-yl)-4-(3-pyridyl)-7*H*-pyrido[2,3:4',5']-thieno[3',2'-*d*] pyrimidin-8-one* ***(11b)***. – Obtained from **10c** as yellow crystals, 0.29 g (74 %) m.p. 233 °C; IR(KBr) ν_{max}/cm^{-1}: 3440 (NH), 1705 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ/ppm: 7.71–7.94 (m, 5H, Ar-H, H-3 pyridine), 7.99–8.96 (m, 6H, H-pyridine, H-6, pyrimidine, NH), 9.61 (s, 1H, NH); MS *m/z*: 396 (M^+, 23 %).

Anal. Calcd. for $C_{21}H_{12}N_6OS$ (M_r = 396.72): C 63.58, H 3.04, N 21.27 %; found: C 63.30, H 2.90, N 21.00 %.

Preparation of ***14a–e***

General Procedure. – To a solution of appropriate **2** (2.0 mmol) in DMF (30 mL) containing a few drops of piperidine, 6–aminouracile or 6-aminothiouracile **12a,b** (2.0 mmol) was added. The reaction mixture was heated under reflux for 6–8 hours. After cooling, the precipitate was collected by filtration and recrystallized from DMF/EtOH.

*7-(1*H*-Benzoimidazol-2-yl)-5-(4-methoxyphenyl)-5,8-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione* ***(14a)***. – Obtained from **2a** and **12a** as yellow crystals, 0.62 g (81 %), m.p. > 350 °C; IR(KBr) ν_{max}/cm^{-1}: 3320 (NH), 1720 cm^{-1} (CO); ^{1}HNMR (DMSO-d_6) δ/ppm: 3.81 (s, 3H, OCH_3), 4.68 (d, 1H, J = 6 Hz, H-5 pyridine), 6.10 (d, 1H, J = 6 Hz, H-6 pyridine), 7.34–7.89 (m, 8H, Ar-H) 8.21 (s, 1H, NH), 10.31, (s,1H, H-8), 10.71(s,1H, H-1),11.32(s,1H, H-3); MS *m/z*: 387 (M^+, 100 %).

Anal. Calcd. for $C_{21}H_{17}N_5O_3$ (M_r = 387.67): C 65.06, H 4.41, N 18.14 %; found: C 64.90, H 4.40, N 18.00 %.

*7-(1*H*-Benzoimidazol-2-yl)-5-(3-pyridyl)-5,8-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione* ***(14b)***. – Obtained from **2c** and **12a** as yellow crystals, 0.56 g (79 %) m.p. > 350 °C; IR(KBr) ν_{max}/cm^{-1}: 3186 (NH), 1720 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 4.76 (d, 1H, H-5 pyridine), 5.93 (d, 1H, H-6 pyridine), 7.24–8.23 (m, 8H, Ar-H, H-pyridine), 8.42 (s, 1H, NH), 10.21, (s,1H, H-8), 10.66 (s,1H, H-1), 11.41 (s, 1H, H-3); MS *m/z:* 358 (M$^+$, 91 %).

Anal. Calcd. for $C_{19}H_{14}N_6O_2$ (M_r = 358.7): C 63.62, H 3.93, N 23.53 %; found: C 63.40, H 3.80, N 23.50 %.

*7-(1*H*-Benzoimidazol-2-yl)-5-(4-nitrophenyl)-5,8-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione* ***(14c)***. – Obtained from **2d** and **12a** as yellowish-brown crystals, 0.57 g (71 %) m.p. > 350 °C; IR(KBr) ν_{max}/cm^{-1}: 3394 (NH), 1701 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 4.79 (d, 1H, CH-5), 5.83 (d, 1H, CH-6), 7.31–8.31 (m, 8H, Ar-H), 8.40 (s, 1H, NH), 10.22 (s, 1H, H-8), 10.42 (s,1H, H-1) and 11.50 (s,1H, H-3).

Anal. Calcd. for $C_{20}H_{14}N_6O_4$ (M_r = 402.69) : C 59.65, H 3.50, N 20.95 %; found: C 59.60, H 3.30, N 20.80 %.

*7-(1*H*-Benzoimidazol-2-yl)-5-(4-methoxyphenyl)-2-thioxo-2,3,5,8-tetrahydro-1*H*-pyrido[2,3-*d*]pyrimidine-4-one* ***(14d)***. – Obtained from **2a** and **12b**, 0.55 g (68 %), as yellow crystals, m.p. 306 °C; IR(KBr) ν_{max}/cm^{-1}: 3421 (NH), 1705 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 3.85 (s, 3H, OCH$_3$), 4.64 (d, 1H, CH-5), 5.98 (d, 1H, CH-6), 7.05–7.8 (m, 8H, Ar-H), 8.00 (s, 1H, NH), 11.78(s, 1H, H-8), 12.52 (s, 1H, H-1) and 13.01(s, 1H, H-3); MS *m/z*: 403 (M$^+$, 100 %).

Anal. Calcd. for $C_{21}H_{17}N_5O_2S$ (M_r = 403.68): C 62.63, H 4.25, N 17.46 %; found: C 62.40, H 4.00, N 17.20 %.

*7-(1*H*-Benzoimidazol-2-yl)-5-(3-pyridyl)-2-thioxo-2,3,5,8-tetrahydro-1*H*-pyrido[2,3-*d*]pyrimidine-4-one* ***(14e)***. – Obtained from **2c** and **12b** as yellow crystals, 0.46 g (62 %) m.p. 337 °C; IR(KBr) ν_{max}/cm^{-1}: 3417 (NH), 1700 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 7.32–8.19 (m, 9H, Ar-H, H-5 pyridine), 8.23 (s, 1H, NH), 11.20 (s, 1H, H-8), 12.31 (s, 1H, H-1) and 13.00 (s, 1H, H-3).

Anal. Calcd. for $C_{19}H_{13}N_6OS$ (M_r = 374.70): C 60.90, H 3.76, N 22.52 %; found: C 60.70, H 3.70, N 22.40 %.

Preparation of ***17a,b***

General Procedure. – Compound **14c,d** (1.0 mmol) in DMF (20 mL) was refluxed for 20–24 hours. The reaction was controlled by TLC until the starting compound completely disappeared. The reaction mixture was cooled, the precipitate was filtered off and recrystallized from DMF/EtOH.

*7-(1*H*-Benzoimidazol-2-yl)-5-(4-nitrophenyl)-1*H*-pyrido[2,3-*d*]-pyrimidine-2,4-dione* ***(17a)***. – Obtained from **14c** as brown crystals, 0.28 g (70 %), m.p. >350 °C; IR(KBr) ν_{max}/cm^{-1}: 3387 (NH), 1689 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 7.32–7.96 (m, 9H, Ar-H, H-6 pyridine), 8.35 (s, 1H, NH), 11.44 (s, 1H, H-1), 11.83 (s, 1H, H-3).

Anal. Calcd. for $C_{20}H_{12}N_6O_4$ (M_r = 400.69): C 59.60, H 3.01, N 21.06 %; found: C 59.50, H 2.80, N 21.00 %.

*7-(1*H*-Benzoimidazol-2-yl)-5-(4-methoxyphenyl)-2-thioxo-2,3-dihydro-1*H*-pyrido-2,3-*d*]pyrimidin-4-one* ***(17b)***. – Obtained from **14d** as yellowish-brown crystals, 0.27 g (72 %), m.p. > 350 °C; IR(KBr) ν_{max}/cm^{-1}: 3334 (NH), 1670 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 3.61(s,3H,OCH$_3$), 7.34–7.95 (m, 9H, Ar-H, H-6 pyridine), 8.23 (s, 1H, NH), 11.14 (s, 1H, H-1) and 11.83 (s, 1H, H-3).

Anal. Calcd. for $C_{21}H_{15}N_5O_2S$ (M_r = 401.67): C 62.80, H 3.76, N 17.51 %; found: C 62.60, H 3.50, N 17.40 %.

*4-Aryl-2,6-bis(1*H*-benzoimidazol-2-yl)pyridine* ***20a–c***

General Procedure. – A mixture of **1** (4.0 mmol), arylaldehyde **18** (2.0 mmol) and ammonium acetate (0.2 g) was heated in an oil bath at 290 °C for 4–8 h. The precipitate, formed on cooling, was treated with cold water (50 mL), collected by filtration and crystallized from the proper solvent.

*2,6-Bis(1*H*-benzoimidazol-2-yl)-4-phenylpyridine* ***(20a)***. – Obtained from **1** and benzaldehyde as yellow crystals from methanol, 0.49 g (58 %) m.p. > 350 °C; IR(KBr) ν_{max}/cm^{-1}: 3325 (NH), 1651 cm^{-1} (C=N); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 7.13–7.68 (m, 13H, Ar-H), 8.01 (s, 2H, H-5, H-3 pyridine), 8.21(s, 2H, 2NH).

Anal. Calcd. for $C_{25}H_{17}N_5$ (M_r = 387.74): C 77.50, H 4.42, N 18.08 %; found: C 77.30, H 4.30, N 17.80 %.

*2,6-Bis(1*H*-benzoimidazol-2yl)-4-(4-methoxyphenyl)pyridine* ***(20b)***. – Obtained from **1** and *p*-methoxybenzaldehyde as yellow crystals from benzene, 0.5 g (61 %) m.p. > 350 °C; IR(KBr) ν_{max}/cm^{-1}: 3394 (NH), 1589 cm^{-1} (C=N); ^{1}H NMR (DMSO-d$_6$) δ/ppm: 3.91 (s, 3H, OCH$_3$), 7.05 (d, 2H, Ar-H), 7.31–7.65 (m, 8H, Ar-H), 7.88–7.91 (d, 2H, Ar-H), 7.94 (s, 2H, 3,5-H-pyridine) and 8.64 (s, 2H, 2NH); MS *m/z* = 417 (M$^+$,100 %).

Anal. Calcd. for $C_{26}H_{19}N_5O$ (M_r = 417.47): C 74.80, H 4.59, N 16.78 %; found: C 74.60, H 4.30, N 16.60 %.

*2,6-Bis(1*H*-benzoimidazol-2yl)-4-(4-chlorophenyl)pyridine* ***(20c)***. – Obtained from **1** and *p*-chlorobenzaldehyde as yellow crystals from benzene, 0.45 g (54 %) m.p. > 350 °C; IR(KBr) ν_{max}/cm^{-1}: 3425 (NH), 1651 cm^{-1} (C=N), ^{1}H NMR (DMSO-d$_6$) δ/ppm: 7.31–7.84(m, 12H, Ar-H), 7.93(s, 2H, 3,5-H-pyridine) and 8.21 (s, 2H, 2NH); MS *m/z*: 421 (M$^+$, 100 %).

Anal. Calcd. for $C_{25}H_{16}N_5Cl$ (M_r = 421.89): C, 71.00, H 3.70, N 16.50 %, found: C 71.17, H 3.82, N 16.60 %.

*3-Aryl -1,5-bis(1*H*-benzoimidazol-2-yl)pentan-1,5-dione* ***(19a,b)***

General Procedure. – To compound **1** (4.0 mmol) in ethanolic sodium hydroxide (15 mL, 10 %), an appropriate arylaldehyde (2.0 mmol) was added dropwise under stirring for 2 h. The resulting precipitate was collected and crystallized from ethanol to afford **19**; heating **19** with NH_4OAc (2.0 mmol) in MeOH for 4 h afforded **20.**

*1,5-Bis(1*H*-Benzoimidazol-2-yl)-3-(4-methoxyphenyl)pentan-1,5-dione* ***(19a)***. – Obtained from **1** and anisaldehyde as yellow crystals, 0.52 g (60 %); m.p. > 320 °C; IR(KBr)

ν_{max}/cm^{-1}: 3348 (NH), 1675 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6) δ/ppm: 3.72 (s, 3H, OCH_3),4.10(m, 1H, CH), 5.40 (d, 4H, $2CH_2$), 7.10–7.93 (m, 12H, Ar-H), 8.51 (s, 2H, 2NH).

Anal. Calcd. for $C_{26}H_{22}N_4O_3$ (M_r = 438.70): C71.19, H 5.05, N 12.82 %; found: C 71.00, H 4.90, N 12.70 %.

*1,5-Bis(1*H*-Benzoimidazol-2-yl)-3-(4-chlorophenyl)pentan-1,5-dione* ***(19b)***. – Obtained from **1** and *p*-chlorobenzaldehyde as yellow crystals from ethanol, 0.55 g (63 %); m.p. > 320 °C; IR(KBr) ν_{max}/cm^{-1}: 3326 (NH), 1681 cm^{-1} (CO); MS *m/z*: 443 (M^+, 62 %).

Anal. Calcd. for $C_{25}H_{19}N_4O_2Cl$ (M_r = 443.17): C 67.76, H 4.32, N 12.69 %; found: C 67.50, H 4.10, N 12.80 %.

CONCLUSION

The applicability and synthetic potency of compound **2** to develop a facile and convenient route to polyfunctional pyridines, thieno[1,2-*b*]pyridines, pyrido[2,3:4',5']thieno[3',2'-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines are reported.

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SAŽETAK

Priprava nekoliko novih piridina, tienopiridina i pirido[2,3:4',5']tieno[3',2'-*d*]pirimidin-8-ona iz 2-acetilbenzoimidazola

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Reakcija 2-acetilbenzoimidazola s nekim arilaldehidima pod različitim uvjetima daje halkon, 1,5-pentandione i piridine. Obrada halkona s različitim reagensima daje nove piridine, tienopiridine i pirido[2,3:4',5']tieno[3',2'-*d*]pirimidin-8-one preko početne adicije metilena ili amino grupe na dvostruku vezu i nakon toga slijedi ciklizacija.