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

Abu Zied. A. Hassanien, a,* El-Sayed. I. Ibrahim, b and Mohamed. E. Afifi a

a Department of Chemistry, Faculty of Education, Suez Canal University, El-Arish, Egypt
b Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, Egypt

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-acetylbenzoimidazole 1 as the key compound in the synthesis of some new heterocycles with potential biological activity.

RESULTS AND DISCUSSION

The key precursor 2-acetylbenzoimidazole 16 was reacted with arylaldehydes to afford chalcone analogues 2.7,8 Treatment of 2 with equimolar amounts of 2-amino-2-methylacrylonitrile in refluxing glacial acetic acid afforded the corresponding 4-aryl-6-(1H-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 C21H18N4O. 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
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-(1H-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-(1H-benzoimidazol-2-yl)-7H-pyrido[2,3-$d$]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$_6$OS.

The reaction of heterocyclic amines and aromatic $\alpha,\beta$-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-
dines 14a–e. These compounds and their oxo and thioxo derivatives reveal interesting biological and physiological properties. 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-d6) spectrum of 14b showed, in addition to the expected signals, two doublets at \(\delta = 4.76\) and 5.93 ppm assigned to H-5 and H-6, respectively, three sharp singlets at \(\delta = 10.21, 10.66\) 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\(_6\)O\(_2\). On the other hand, prolonged reaction time to over 20 hours gave 17a,b; the conversion was controlled by TLC. The 1H NMR (DMSO-d6) of 17a revealed, in addition to the expected signals, singlets at \(\delta = 7.26, 11.44\) and 11.83 ppm corresponding 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\(_2\)OAc, 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 1H NMR (DMSO-d6) spectrum of 20b showed, in addition to the expected signals, a singlet at \(\delta = 3.91\) 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\(_5\)O. 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\(_2\)OAc 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-d6 and/or CDCl\(_3\)-d\(_3\) 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 chromatography.
phy was carried out on 5×20 cm plates coated with silica gel GF 254 type 60, mesh size 50–250. Compounds 1 and 2 were prepared according to the reported method.

4-Aryl-6-(1H-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-(1H-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) $\nu_{\text{max}}$/cm$^{-1}$: 3386 (NH), 2221 (CN); $^1$H NMR (DMSO-d$_6$) $\delta$/ppm: 2.5 (s, 3H, CH$_3$), 3.85 (s, 3H, OCH$_3$), 4.6 (d, J = 6.2 Hz, 1H, H-5 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$_4$O (Mr = 342.63): C 73.62, H 5.29, N 16.42 %; found: C 73.70, H 5.00, N 16.20 %.

6-(1H-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) $\nu_{\text{max}}$/cm$^{-1}$: 3332 (NH), 2221 (CN). $^1$H NMR (DMSO-d$_6$) $\delta$/ppm: 2.2 (s, 3H, CH$_3$), 4.6 (d, J = 6.2 Hz, 1H, H-5 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$_4$Cl (Mr = 347.09): C 69.21, H 4.35, N 16.21 %; found: C 69.30, H 4.10, N 16.10 %.

6-(1H-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.


254 °C; IR (KBr) ν_{max}/cm⁻¹: 3349 (NH), 2200 (C=N); ¹H NMR (DMSO-d₆) δ/ppm: 2.31 (s, 3H, CH₃), 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).

**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-(1H-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: 3345 (NH), 2237 (C=N), 1267 (C=S); ¹H NMR (DMSO-d₆) δ/ppm: 3.88 (s, 3H, OCH₃), 7.16–7.81 (m, 8H, Ar-H), 8.21 (s, 1H, H-5 pyridine), 8.44 (s, 1H, NH) and 9.30 (s, 1H, NH pyridine).

**Anal.** Calcd. for C_{20}H_{15}N_{5}O_{2} (Mr = 357.66): C 67.17, H 4.22, N 19.66 %; found: C 67.10, H 4.00, N 19.50 %.

6-(1H-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. 306 °C; IR(KBr) ν_{max}/cm⁻¹: 3456 (NH), 2237 (C=N), 1267 (C=S); ¹H NMR (DMSO-d₆) 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_{4}SCl (Mr = 363.16): C 62.86, H 3.05, N 15.50 %; found: C 62.70, H 2.90, N 15.30 %.

6-(1H-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_{5}S (Mr = 329.62): C 65.59, H 3.36, N 21.34 %; found: C 65.50, H 3.30, N 21.10 %.

6-(1H-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); ¹H NMR (DMSO-d₆) 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_{5}O_{2}S (Mr = 373.62): C 61.08, H 2.96, N 18.82 %; found: C 60.80, H 2.90, N 18.60 %.

4-Aryl-6-(1H-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 alkyllating 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-(1H-Benzimidazol-2-yl)-3-cyano-4-(4-methoxyphenyl)-pyridin-2-yl-sulfanyl]acetic acid ethyl ester (9a). – Obtained from 7a and ethyl bromoacetyl as pale yellow crystals from benzene; 0.70 g (79 %), m.p. 229 °C; IR(KBr) max/cm–1: 3355 (NH), 2216 (C=O); 1H NMR (CDCl3) δ/ppm: 3.56 (s, 3H, OCH3), 7.25–7.90 (m, 9H, Ar-H, H-5 pyridine), 8.27 (s, 1H, NH); MS m/z: 476 (M+, 100 %).

6-(1H-Benzimidazol-2-yl)-4-(4-chlorophenyl]pyridin-2-yl-sulfanyl] phenethanone (9b). – Obtained from 7b and phenacyl bromide as yellow crystals from benzene; 0.71 g (74 %), m.p. 241 °C; IR(KBr) max/cm–1: 3355 (NH), 2221 (C=CN), 1705 (CO); 1H NMR (CDCl3) δ/ppm: 3.89 (s, 3H, OCH3), 7.24–7.98 (m, 9H, Ar-H, H-5 pyridine), 8.2 (s, 1H, NH); MS m/z: 444 (M+, 100 %).

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-(1H-benzimidazol-2-yl)-4-(4-methoxyphenyl)thieno[2,3-b]pyridine-2-carboxylic acid ethyl ester (10a). – Obtained from 7a and ethyl bromoacetyl as yellow crystals; 0.65 g (74 %) m.p. 285 °C; IR(KBr) max/cm–1: 3355 (NH), 2221 (C–CN), 1705 (CO); 1H NMR (CDCl3) δ/ppm: 1.2 (t, 3H, J = 7 Hz, CH3), 3.70 (s, 2H, NH2), 7.0–7.9 (m, 9H, Ar-H), and 8.2 (s, 1H, NH); MS m/z: 241 (M+, 36 %).

Anal. Calcd. for C27H17N4OClS (M = 455.69): C 63.57, H 4.12, N 16.92 %; found: C 63.50, H 4.00, N 16.70 %.

3-Amino-6-(1H-benzimidazol-2-yl)-4-(4-methoxyphenyl] thieno[2,3-b]pyridine-2-phenylmethane (10d). – Obtained from 7a and phenacyl bromide as yellow crystals from benzene; 0.66 g (70 %); m.p. 173 °C; IR(KBr) max/cm–1: 3320–3473 (NH), 1700 (CO), 1H NMR (CDCl3) δ/ppm: 3.93 (s, 3H, OCH3), 5.82 (s, 2H, NH2), 7.26–7.9 (m, 14H, Ar-H, H-5 pyridine), 8.27 (s, 1H, NH); MS m/z: 476 (M+, 100 %).

General Procedure. – Compound 10a (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.

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

To a solution of appropriate 10 (2.0 mmol) in DMF (30 mL) containing a few drops of piperidine, 6-aminouracile or 6-aminothiouracile was added. The reaction mixture 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.

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.

Anal. Calcd. for C31H17N3O3 (M_+ = 387.67): C 65.06, H 4.41, N 18.14 %; found: C 64.90, H 4.40, N 18.00 %.

7-(1H-Benzimidazol-2-yl)-5-(3-pyridyl)-8,5-dihydro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (14b). – Obtained from 2c and 12a as yellow crystals, 0.57 g (71 %) m.p. > 350 °C; IR(KBr) _ν_ max/cm⁻¹: 3216 (NH), 1670 cm⁻¹ (CO); 1H NMR (DMSO-d₆) δ/ppm: 7.91–7.83 (m, 1H, H-5 pyridine), 7.24–7.22 (m, 2H, Ar-H), 8.31 (s, 1H, H-3 pyridine), 8.00 (s, 2H, H-5, H-3 pyridine), 8.23 (s, 1H, H-1), 11.90 (s, 1H, H-3). Anal. Calcd. for C26H19N5O4 (M_+ = 403.68): C 72.60, H 4.70, N 18.70 %; found: C 72.60, H 4.50, N 18.60 %.

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-(1H-Benzimidazol-2-yl)-5-(4-nitrophenyl)-1H-pyridazin-3-ol (17a). – Obtained from 14c as brown crystals, 0.28 g (79 %) m.p. > 350 °C; IR(KBr) 1598 cm⁻¹ (NO_{2}); 1H NMR (DMSO-d₆) δ/ppm: 8.33–8.30 (m, 2H, Ar-H), 8.00–7.97 (m, 2H, Ar-H), 7.20–7.15 (m, 1H, Ar-H, H-5 pyrimidine), 7.75 (s, 1H, H-1), 7.70 (s, 1H, H-3). Anal. Calcd. for C21H15N5O2S (M_+ = 387.67): C 59.60, H 3.01, N 23.53 %; found: C 59.60, H 3.00, N 23.50 %.

General Procedure. – Compound 14b (1.0 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 NH₃·H₂OAc (2.0 mmol) in MeOH for 4 h afforded 20.

3-Aryl-1,5-bis[(1H-benzimidazol-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 NH₃·H₂OAc (2.0 mmol) in MeOH for 4 h afforded 20.

7-(1H-Benzimidazol-2-yl)-5-(4-methoxyphenyl)-2-thioxo-2,3-dihydro-1H-pyrido[2,3-d]pyrimidin-4-one (17b). – Obtained from 14d as yellow-brown crystals, 0.27 g (72 %) m.p. > 350 °C; IR(KBr) 1670 cm⁻¹ (CO); 1H NMR (DMSO-d₆) δ/ppm: 7.93 (s, 1H, H-8), 12.54 (s, 1H, H-1). Anal. Calcd. for C21H15N5O3 (M_+ = 387.74): C 77.50, H 4.42, N 18.08 %; found: C 77.30, H 4.30, N 17.80 %.

7-(1H-Benzimidazol-2-yl)-5-(4-nitrophenyl)-2-thioxo-2,3-dihydro-1H-pyridazin-3-ol (17c). – Obtained from 14c as brown crystals, 0.49 g (58 %) m.p. > 350 °C; IR(KBr) 1587 cm⁻¹ (CO); 1H NMR (DMSO-d₆) δ/ppm: 8.06 (s, 1H, H-8), 12.51 (s, 1H, H-1). Anal. Calcd. for C26H19N5O4 (M_+ = 403.68): C 72.60, H 4.70, N 18.70 %; found: C 72.60, H 4.50, N 18.60 %.
\[ \nu_{\text{max}} / \text{cm}^{-1}: \] 3348 (NH), 1675 cm\(^{-1}\) (CO); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta/\text{ppm}:\) 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\(_4\)O\(_3\) (\(\text{Mr} = 438.70\)): C 71.19, H 5.05, N 12.82 %; found: C 71.00, H 4.90, N 12.70 %.

**CONCLUSION**

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

**REFERENCES**


**SAŽETAK**

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

Abu Zied A. Hassani, El-Sayed I. Ibrahim i Mohamed E. Afifi

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']thieno[3',2'-d]pirimidin-8-one preko početne adicije metilena ili amino grupe na dvostruku vezu i nakon toga slijedi ciklizacija.