
Abdou O Abdelhamid*, Hussein F Zohdi & Mahmoud M Ziaa

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt; e-mail: ABDOU@main-scc.cairo.eg.

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Thieno[2″,3‴:5′,1′]pyrimido[1,6-a]benzimidazoles 21-47 have been synthesized by the reaction of 3-mercapto[1,6-a]benzimidazole with halo ketones and halo esters, respectively. 3-Aminopyrazolo[3‴,4‴:5,6]pyrimido[1,6-a]benzimidazole 9 reacted with acetylaceon, ethyl acetoacetate, ethyl benzoylecetate, ethyl α-chloroacetoacetate and β-aryl-α-cyanoacrylonitriles to give pyrimido[2″,3‴:5′,1′]pyrazolo[3″,4‴:4,5]pyrimido[1,6-a]benzimidazoles 13, 14a,b, 15, 19a-e, respectively. Diazonium salt 20 reacted with each of malononitrile, benzoylecetone, ethylene glycol, diethylmalonate and β-keto esters to give [1,2,4]triazino[3″,4‴:5′,1′]pyrazolo[3″,4‴:4,5]pyrimido[6,1-a]benzimidazoles 21-25a,b, respectively. Structures of the synthesized compounds are confirmed on the basis of elemental analyses, and spectral data.

Several fused benzimidazoles are known to possess antimicrobial, anti-inflammatory and anticancer activities. In continuation of our interest in the synthesis of heterocycles, we report herein the synthesis of compounds containing the benzimidazole moiety.

The reaction of 2-[(1-ethoxycarbonyl)benzimidazol-2-yl]acetonitrile 2 with equimolar amounts of phenyl isothiocyanate and potassium hydroxide, in N,N-dimethylformamide afforded the potassium salt of 4-cyano-3-mercapto-1-oxo-2-phenylpyrimidino[1,6-a]benzimidazole 2, which converted to the thiolid 3 by acetic acid (cf. Scheme I). Structure 3 was elucidated on the basis of microanalyses, spectroscopic data and chemical transformation. The IR (cm⁻¹) spectrum of 3 revealed absorption bands at 2227 (CN) and 1720 (CO). Its 1H NMR spectrum showed only a multiplet at δ 7.25-8.22 ppm for the aromatic and thioli protons.

Compound 2 reacted with chloroacetone to yield a product formulated as 2-acetyle-3-amino-10-oxo-11-phenylthiino[2″,3‴:4,5]pyrimido[1,6-a]benzimidazole 4 on the basis of elemental analyses and spectral data. IR (cm⁻¹) spectrum of 4 revealed absorption bands at 3457, 3316 (NH₂); 1719, 1678 (CO) and no absorption band was observed at 2000-2300 showing the absence of the CN group. The 1H NMR spectrum showed signals at δ 2.15 (s, 3H, CH₃CO) and 7.38-8.26 (m, 11H, ArH's and NH₂ exchangeable).

Also, compound 2 reacted with ethyl chloroacetate to give a product with molecular formula C₂₆H₂₆N₅O₅S. The IR (cm⁻¹) spectrum revealed absorption bands at 3460, 3347 (NH₂) and 1715, 1678 (CO). Its 1H NMR spectrum showed signals at δ 1.33 (t, 3H, CH₃CH₂), 3.17 (CH₂CH₃) and 7.03-8.32 (m, 11H, ArH's and NH₂). On the basis of these data, the product was formulated as 3-amino-2-ethoxycarbonyl-10-oxo-11-phenylthiino[2″,3‴:4,5]pyrimido[1,6-a]benzimidazole 5 (cf. Scheme I). Alternatively, compound 2 reacted with each of 3-chloro-2,4-pentanedione and ethyl 2-chloro-3-oxobutanoate to give the products identical in all respects (mp, mixed mp and spectral data) with corresponding 4 and 5, respectively (cf. Scheme I).

Similarly, compound 3 reacted with 2-aryl-1-bromoethan-2-one, chloroacetanitrite and methyl iodide to give 3-amino-2-aryl-10-oxo-11-arylthiino[2″,3‴:4,5]pyrimido[1,6-a]benzimidazoles 6a,b, 3-amino-2-cyano-10-oxo-11-phenylthiino[2″,3‴:4,5]pyrimido[1,6-a]benzimidazole 7 and 3-thiomethylpyrimido[1,6-a]benzimidazole derivative 8, respectively. Structures of 6, 7 and 8 were confirmed on the basis of spectral data. The, IR (cm⁻¹) spectrum of 7 revealed bands at 3451, 3350, 3217(NH₂), 2176(CN), 1703(CO) and its 1H NMR spectrum showed signals at δ 7.29-7.81 (m, 9H, ArH’s) and 8.42 (s, br, 2H, NH₂). IR (cm⁻¹) spectrum of 8 revealed absorption bands at 2228(CN), 1720(CO) and 1610(C=O). Its 1H
NMR spectrum showed signals at δ 2.70 (s, 3H, SCH₃) and 7.36-8.22 (m, 9H, ArH's). Compound 8 reacted with hydrazine hydrate to afford a sulfur free product, which showed absorption bands in the IR (cm⁻¹) spectrum at 3295, 3171 (NH₂) and 1710 (CO). 

Similarly, the reaction of compound 9 with ethyl acetoacetate (or acetoacetyl chloride) and ethyl benzoylacacetate (or ethyl benzoylacetate) in boiling acetic acid produced products and were formulated as 2, 8-dioxo-7-phenyl-4-substituted-pyrimido[2'',3'':5'',6']pyrazolo[3',4':5,6]pyrimido[1,6-a]benzimidazoles 14a, b, respectively based on the spectral data. 

3-Aminopyrazolo[3',4':5,6]pyrimido[1,6-a]benzimidazole 9 reacted with each of acetylacetone, ethyl acetoacetate, (or acetoacetanilide), and ethyl benzoylacacetate (or benzoylacetanilide) to afford pentacyclic derivatives 13 and 14a,b, respectively (cf. Scheme II). Thus, compound 9 reacted with acetylacetone to give 2,4-dimethyl-8-oxo-7-phenylpyrimido[2'',3'':5'',6'']pyrazolo[3',4':4,5]pyrimido[1,6-a]benzimidazole 13. Its IR spectrum revealed the absence of any absorption bands due to amino group and showed carbonyl absorption at 1667 cm⁻¹. The ¹H NMR spectrum of 13 showed signals at δ 2.44 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 6.61 (s, 1H, pyrimidine H-5) and 7.31-8.31 (m, 9H, ArH's).
in each case, a single product according to TLC. Based on analytical data, two isomeric structures, 17 or 19 are possible (cf. Scheme II). The IR (cm⁻¹) spectra of the products showed absorption bands for the NH and NH₂ groups in the region 3450-3170, the cyano absorption around 2200 cm⁻¹ and the carbonyl at 1720. ¹H NMR spectrum of the product, obtained from the reaction of 9 with 16b, showed signals at δ 3.87(s, 3H, CH₃OC₆H₄), 5.37(s, 1H, pyrimidine H-4), 6.88(s, br., 2H, NH₂, exchangeable with D₂O), 7.28-7.92(m, 12H, ArH's), 8.21(d, 1H, ArH) and 9.32(s, br., 1H, NH). Spectroscopic data could not distinguish between these two possible regioisomers 17 and 19 but the structure 19 is the most likely⁶. The formation of 19a-e is assumed to proceed via initial attack of the exocyclic amino group of 9 on the activated double bond of 16 to yield the acyclic intermediate 18, which then undergoes intramolecular cyclization to afford the pyrimido[2'₅',4'₅]pyrazolo[3',4':4,5]pyrimido[6,1-a]benzimidazoles 19a-e.

Diazonium chloride 20 coupled with malononitrile in ethanolic sodium acetate solution to give a product showing absorption bands at 3286, 3112(NH₂), 2224(CN) and 1653(CO) in its IR (cm⁻¹) spectrum. Its ¹H NMR spectrum showed signals at δ 7.42-7.96(m, 9H, ArH's) and 9.35(s, br., 2H, NH₂). This compound was formulated as 4-aminom-3-cyano-7-phenyl-[1,2,4]triazino[3'₅,4'₅:5',6']pyrazolo[3',4':4,5]pyrimido[6,1-a]benzimidazole 21.

Similarly, compound 20 coupled with each of benzoylacetonitrile, acetylacetone, diethyl malonate, ethyl acetocetate and ethyl benzoacetate, in ethanolic sodium acetate solution to afford directly the corresponding 1,2,4-triazino[3'₅,4'₅:5',6']pyrazolo[3',4':4,5]pyrimido[6,1-a]benzimidazoles 22-25a,b (cf. Scheme III). Structures 22-25 were confirmed on the basis of elemental analyses and spectral data. The IR (cm⁻¹) spectrum of 22 showed cyano absorption band at 2192. Also, IR (cm⁻¹) spectrum of 25a revealed absorption bands at 1717 and 1664(2CO's). Its ¹H NMR spectrum showed signals at δ 1.03(t, 3H, CH₂CH₃), 1.95(s, 3H, CH₃), 4.22(q, 2H, CH₂CH₃) and 7.01-7.75(m, 9H, ArH's). Its ¹H NMR spectrum of 25b showed signals at δ 1.04(t, 3H, CH₂CH₃), 4.22(q, 2H, CH₂CH₃) and 7.44-8.34(m, 14H, ArH's).
Experimental Section

All melting points were determined on a MELTEMP II melting point apparatus and are uncorrected. IR spectra were recorded (KBr) on a Shimadzu FT-IR 8201 PC spectrophotometer; \(^1\)H NMR spectra on a Varian Gemini 200 MHz spectrometer (chemical shifts in \(\delta\), ppm) using TMS as internal reference; and mass spectra on a Shimadzu mass spectrometer, GC-MS QP1000 EX, operating at 70 eV. Microanalytical data was carried out at the Microanalytical Center, Cairo University. 2-[(1-Ethoxycarbonyl)benzimidazol-2-yl] acetone nitrile 1 was prepared as reported earlier\(^2\).

Pyrimido[1,6-\(a\)]benzimidazoles 2, 3 and 8. A mixture of 1 (2.29 g, 0.01 mole), phenyl isothiocyanate (1.35 g, 0.01 mole) and potassium hydroxide (0.56 g, 0.01 mole) in dimethylformamide (20 mL) was stirred at room temperature for 2 hr. The reaction mixture was divided into two parts, the first part was diluted with water (10 mL) and acidified with acetic acid to give the thiol derivative 3. Methyl iodide (0.32 mL, 0.005 mole) was added to the second part with stirring at room temperature for 2 hr. The resulting solid was collected and crystallized from acetic acid to give the S-methyl derivative 8 (cf. Table I).

3-Amino-2-substituted-10-oxo-11-phenylthieno[2',3':4,5]pyrimido[1,6-\(a\)]benzimidazoles 4-7. A mixture of 1 (1.15 g, 0.005 mole), potassium hydroxide (0.28 g, 0.005 mole) and phenyl isothiocyanate (0.67 g, 0.005 mole) in dimethylformamide (20 mL) was stirred at room temperature for 2 hr. The appropriate reagents [chloroacetone (or 3-chloro-2,4-pentandione), ethyl chloroacetate (or ethyl 2-chloro-3-oxobutanate), o-bromoacetophenones and chloroacetonitrile] (0.005 mole) was added with stirring and stirring was continued for 1 hr. The solid obtained was washed with water and crystallized from dimethylformamide to give 4-7, respectively (cf. Table I).

1-Amino-10-oxo-11-pyrazolo[3',4':5,6]pyrimido-[1,6-\(a\)]benzimidazole 9. A mixture of S-methyl derivative 8 (3.32 g, 0.01 mole) and hydrazine hydrate (1 mL, 99%, 0.02 mole) in ethanol (20 mL) was refluxed for 5 hr. The solid obtained was crystallized from acetic acid to give 9 (cf. Table I).

Pyrimido[2',3':5',1']pyrazolo[3',4':4,5]pyrimido-[1,6-\(a\)]benzimidazoles 13, 14a,b and 15. A mixture of the appropriate acetylacetone, ethyl acetoacetate (or acetoacetanilide), ethyl benzoylacetae and ethyl 2-chloro-3-oxobutanate (0.005 mole) and aminopyrazole 9 (1.5 g, 0.005 mole) in acetic acid (15 mL) was refluxed for 4 hr. The resulting solid was collected, washed with water and then crystallized from acetic acid or dimethylformamide to give 13, 14a,b and 15, respectively (cf. Table I).

Pyrimido[2',3':5',1']pyrazolo[3',4':4,5]pyrimido-[1,6-\(a\)]benzimidazoles 19a-e. Equimolar amounts of
aminopyrazole 9 (1.5 g, 0.005 mole) and the appropriate 2-aryl-1-cyanoacetonitrile 16a-e (0.005 mole) in ethanol (25 mL) containing piperidine (two drops) was refluxed for 4 hr. The resulting solid was collected and crystallized from acetic acid or dimethylformamide to give 19a-e, respectively (cf. Table I).

Triazino[3"',4"':5',1']pyrazolo[3',4':4,5]pyrimido[6,1-a]benzimidazoles 21-25a,b. Aminopyrazole-diazonium chloride 20 (0.01 mole) [Sodium nitrite
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(0.7 g, 0.01 mole) in water (5 mL)] was added dropwise with stirring at 0-5°C to a solution of 9 (3.2 g, 0.01 mole) in a mixture of acetic acid (2 mL) and hydrochloric acid (3 mL, 12 M)] was added to a cold solution of each of malononitrile, benzoylecyanitrile, acetylacetonitrile, diethyl malonate, ethyl acetoacetate or ethyl benzoylecyanacetate (0.01 mole) in ethanol (50 mL) containing sodium acetate trihydrate (1.3 g, 0.01 mole). The reaction mixture was stirred for 5 hr and the precipitated products were filtered off, washed with water, dried and crystallized from ethanol to give 21-25a,b, respectively.

References