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New polycyclic azines derived from pyrazolo[3,4-*b*]pyridine

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The aminoimidazolinyl derivative **3** was synthesized using the pyrazole amino aldehyde **1** as a starting material. Compound **3** has been used as a key intermediate in the synthesis of the title compounds.

1. Introduction

Pyrazolo[3,4-*b*]pyridines proved to be an interesting class of heterocycles. They act as selective serotinin re-uptake inhibitors [1, 2], corticotrpin-releasing factor (CRF) antagonists in treating cardiovascular diseases, osteoporosis, ulcers [3] and they are effective in the treatment of a wide range of stress related illness such as depression, anxiety, headache, irritable bowel syndrome, inflammatory diseases, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhagic stress, drug addiction and infertility [4]. Also they show analgesic and antinociceptive activity [5]. They are Platelet aggregation inhibitors [6] and enhance phagocytosis of leukocytes [7]. They are used as drugs for treatment of pancytopenia [8], thrombocytopenia and erythropenia [9].

2. Investigations, results and discussion

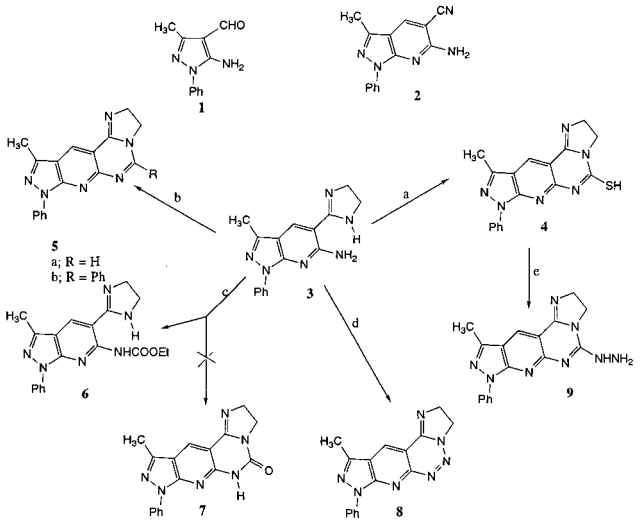
With all the above facts in mind and in continuation of our previous work directed to the synthesis of new heterocycles of potential biological activities [10–12], we report herein the synthesis of new imidazopyrazolopyridopyrimidines.

In earlier papers we have reported the synthesis of imidazopyrimidines fused to a pyrazole ring [13] and to a pyridazine ring [14]. In this paper the synthesis of imidazopyrimidines fused to a pyrazolo pyridine moiety and its related derivatives are described.

The readily available pyrazole aminoaldehyde **1** [15] was interacted with malononitrile in boiling ethanol containing a few drops of piperidine to give the 6-amino−3-methyl-1-phenyl-1 *H*-pyrazolo[3,4-b]pyridine-5-carbonitrile **2** [16, 17]. The cyano group of the latter compound was transformed into a imidazolinyl group via the interaction with ethylene diamine in the presence of carbon disulfide using a procedure analogous to that reported earlier [13]. The resulting amino imidazolinylpyrazolopyridine **3** was used as a key intermediate in the synthesis of the target imidazopyrazolopyridopyrimidines.

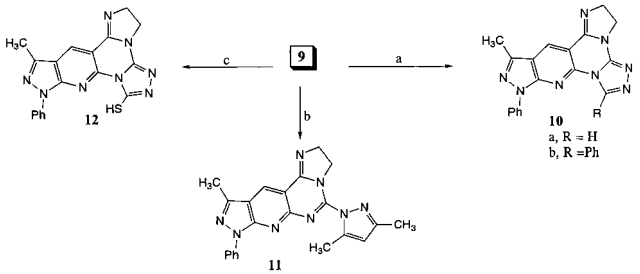
Thus, compound **3** was interacted with carbon disulfide in pyridine to give the thione **4** (Scheme 1). The derivatives **5a**, **b**, were obtained when **3** was allowed to react with formic acid and benzoyl chloride respectively. However, when **3** was allowed to react with ethylchloroformate the product was analyzed for the imidazolinyl derivative **6** instead of the possible oxopyrimidine **7**. The treatment of **3** with nitrous acid afforded the triazine **8**. On the other hand the mercapto group of **4** could be displaced by a hydrazino function to give the hydrazino compound **9**. This hydrazino derivative proved to be a versatile compound in synthetic realizations (Scheme 2). The hydrazino group of **9** was converted into the dimethyl pyrazolyl derivative **11** upon reaction with acetylacetone. Moreover, **9** could be transformed into the pentacyclic heterocycles **10a**, **b** and **12.** Compound **10a** was obtained when **9** was reacted with formic acid, while compound **10b** was formed via the interaction of **9** with benzoyl chloride in pyridine. The thione derivative **12** was obtained when **9** was interacted with carbon disulfide in pyridine.

Scheme 1



a; CS_2/pyridine, b; HCOOH/AcONa (5a); PhCOCl/pyridine (5b), c; ClCOOEt, d; HNO_2, e; NH_2NH_2

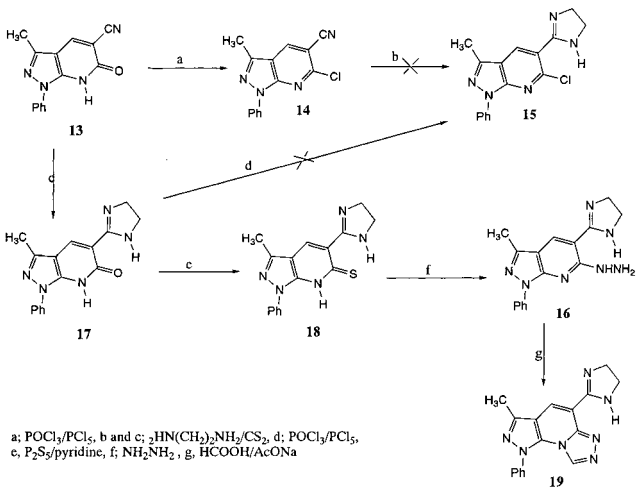
Scheme 2



a; HCOOH/AcONa (10a); PhCOCl/pyridine (10b), b; $CH_2(COCH_3)_2$, d; CS_2/pyridine

On the other hand, the treatment of the cyanopyrazolopyridone **13** [15] with a mixture of phosphoryl chloride and phosphorus pentachloride gave the chloro nitrile **14** (Scheme 3). One of the strategies for preparing the hydrazino derivative **16** is to transform **14** into **15** followed by the treatment of the latter compound with hydrazine hydrate. However, attempts to transform the cyano function of compound **14** into imidazolinyl group to give **15** were unsuccessful and an ill-defined compound was produced. An alternative route to obtain **15** could be envisaged through the transformation of **13** into **17** using our usual procedure [13] followed by treatment the latter compound with phosphoryl chloride. However, the last reaction also

Scheme 3



failed to proceed. It is worth to mention that the only successful route to obtain **16** was found to be via the transformation of the imidazolinypyrazolopyridone **17** into the corresponding thione **18,** upon reaction with phosphorous pentasulfide in pyridine, which was subsequently treated with hydrazine hydrate. The pyrazolotriazolopyridine derivative **19** resulted when **16** was allowed to interact with formic acid in the presence of sodium acetate.

3. Experimental

All m.p.'s are uncorrected and were measured on a Mel-Temp II apparatus. IR spectra were run on a Pye-Unicam SP3-100 spectrophotometer in KBr discs. ^{1}H NMR spectra were recorded on a 90 MHz Varian EM 390 NMR spectrometer in the suitable deuterated solvent using TMS as an internal standard. The elemental analyses were carried out on a Perkin Elmer 240 C elemental analyzer and the results were within $\pm$ 0.4% of the calculated values. Compounds **1** [15], **13** [15] and **2** [16] were prepared following known procedures.

3.1. 6-Amino-5-(4,5-dihydroimidazol-2-yl)-3-methyl-1-phenylpyrazolo[3,4-b] pyridine (**3**)

A mixture of the aminocarbonitrile **2** (4.98 g, 0.02 mol), ethylene diamine (15 ml) and CS_2 (1 ml) was heated under reflux on a water bath for 6 h. After cooling the reaction mixture was poured into H_2O and the precipitate obtained was filtered, washed with H_2O, dried and crystallized from C_2H_5OH to give pale yellow needles, m.p. 207 °C, yield 4.5 g (78%). IR: ν cm^{-1} 3420–3250 (NH_2 & NH).^{1}H NMR (CF_3COOD): δ 2.77 (s, 3 H, CH_3), 4.4 (s, 4H, 2 CH_2-imidazoline), 7.7 (m, 5H, Ar-H), 8.83 (s, 1 H, pyridine).
$C_{16}H_{16}N_6$ (292.2)

3.2. 2,3-Dihydro-10-methyl-8-phenyl-8 H-pyrazolo[4′,3′:5,6]pyrido[3,2-e]-imidazo[1,2-c]pyrimidin-5(6H)-thione (**4**)

A mixture of 3 (2.92 g, 0.01 mol) and CS_2 (15 ml) in dry pyridine (50 ml) was heated under reflux for 50 h. The solid product formed on hot was filtered, washed with H_2O, dried and crystallized from dioxane-H_2O (2 : 1) to give a small cream needles, m.p. 345–347 °C, yield 2.1 g (64%). IR: ν cm^{-1} 3150 (NH). ^{1}H NMR (CF_3COOD): δ 2.93 (s, 3 H, CH_3), 4.5 (m, 2 H, CH_2-imidazoline), 4.77 (m, 2 H, CH_2-imidazoline), 7.73 (m, 5H, Ar-H), 9.33 (s, 1 H, pyridine).
$C_{17}H_{14}N_6S$ (334.3)

3.3. 2,3-Dihydro-10-methyl-8-phenyl-8H-pyrazolo[4′,3′:5,6]pyrido[3,2-e]-imidazo[1,2-c]pyrimidine (**5a**)

A mixture of compound **3** (0.58 g, 0.002 mol) and fused CH_3COONa (0.5 g) in HCOOH (25 ml) was heated under reflux for 8 hrs. The cold reaction mixture was then poured into cold H_2O and then was stirred at room temperature for 5 h. The solid product was crystallized from DMF-H_2O (1 : 1) to give pale yellow crystals, m.p. > 360 °C, yield 0.3 g (50%). IR: ν cm^1 3050 (CH arom.), 2920 (CH aliph.).^{1}H NMR (DMSO.d_6): δ 2.6 (s, 3H, CH_3), , 4.1 (s, 4H, 2 CH_2-imidazoline), 7.33 (m, 3 H, Ar-H), 7.9 (s, 1 H, pyrimidine), 8.33 (m, 2 H, Ar-H), 8.63 (s, 1 H, pyridine).
$C_{17}H_{14}N_6$ (302.3)

3.4. 2,3-Dihydro-5,8-diphenyl-10-methyl-8H-pyrazolo[4′,3′:5,6]pyrido-[3,2-e]imidazo[1,2-c]pyrimidine (**5b**)

A mixture of compound **3** (0.58 g, 0.002 mol) and C_6H_5COCl (0.3 g, 0.002 mol) in dry pyridine (25 ml) was heated under reflux for 2 h. The solid product obtained after cooling the reaction mixture was filtered, washed with H_2O, dried and recrystallized from DMF-H_2O (4 : 1) to give yellowish-orange needles, m.p. > 360 °C, yield 0.54 g (71%). IR: ν cm^{-1} 3000 (CH arom.), 2900 (CH aliph.).^{1}H NMR (CF_3COOD): δ 2.9 (s, 3 H, CH_3), 4.6–4.8 (m, 2 H, CH_2-imidazoline), 4.9–5.1 (m, 2 H, CH_2-imidazoline), 7.6–8 (m, 10 H, Ar-H), 9.7 (s, 1 H, pyridine).
$C_{23}H_{18}N_6$ (378.4)

3.5. Ethyl N-(5-(2-imidazolin-2-yl)-3-methyl-1-phenylpyrazolo[3,4-b]pyridin-6-yl)-carbamate (**6**)

To a solution of **3** (0.58 g, 0.002 mol) and $ClCOOC_2H_5$ (0.22 g, 0.002 mol) in dry pyridine (15 ml) was heated under reflux for 5 h. The cold reaction mixture was poured into H_2O and the solid precipitate was collected washed with H_2O, dried and crystallized from dioxane-H_2O (4 : 1) to give yellow crystals, m.p. 250–252 °C, yield, 0.4 g (58%). IR: ν cm^{-1} 3300 (NH), 1710 (CO). ^{1}H NMR ($CDCl_3$): δ 1.1–1.25 (t 3 H, $\underline{CH_3}CH_2$), 2.7 (s, 3 H, CH_3), 3.4 (m, 4 H, 2 CH_2-imidazoline), 3.9–4.1 (q, 2 H, $CH_3\underline{CH_2}$), 7.3–8.3 (m, 5 H, Ar-H), 8,85 (s, 1 H, pyridine).
$C_{19}H_{20}N_6O_2$ (364.4)

3.6. 2,3-Dihydro-10-methyl-8-phenyl-8Hpyrazolo[4′,3′:5,6]pyrido[3,2-e] imidazo[1,2-c]-1,2,3-triazine (**8**)

To a solution of **3** (0.58 g, 0.002 mol) in CH_3COOH 20 ml, $NaNO_2$ solution (0.2 g, 0.003 mol) in 3 ml H_2O was added dropwise with stirring at room temperature. The solid product formed was collected and crystallized from DMF-H_2O (1 : 1) to give pale yellow crystals m.p. > 360 °C, yield 0.46 g (76%). IR: ν cm^{-1} 3050 (CH arom.), 2900 (CH aliph.).^{1}H NMR (CF_3COOD): δ 2.97 (s, 3H, CH_3), 4.67 (m, 2 H, CH_2-imidazoline), 5.27 (m, 2 H, CH_2-imidazoline), 7.67 (m, 3 H, Ar-H), 7.83 (m, 2 H, Ar-H), 9.63 (s, 1H, pyridine).
$C_{16}H_{13}N_7$ (303.3)

3.7. 2,3-Dihydro-5-hydrazino-10-methyl-8-phenyl-8H-pyrazolo[4′,3′:5,6] pyrido[3,2-e]imidazo[1,2-c]pyrimidine (**9**)

A mixture of the thione 4 (3.34 g, 0.01 mol) and excess hydrazine hydrate (3 ml, 80%) in dry pyridine (50 ml) was heated under reflux for 8 h. The solid product was filtered, washed with H_2O, dried and crystallized from dioxane to give small pale-yellow needles, m.p. >360 °C, yield 2.3 g (70%). IR: ν cm^{-1} 3380, 3200 ($NHNH_2$). ^{1}H NMR (CF_3COOD): δ 2.90 (s, 3 H, CH_3), 4.73 (m, 4H, 2 CH_2-imidazoline), 7.7 (s, 5 H, Ar-H), 9.5 (s, 1H, pyridine).
$C_{17}H_{16}N_8$ (332.4)

3.8. 2,3-Dihydro-12-methyl-10-phenyl-10H-pyrazolo[4′,3′:5,6]pyrido[3,2-e] imidazo[1,2-c]-1,2,4- triazolo[4,3-a]pyrimidine (**10a**)

A mixture of compound **9** (0.66 g, 0.002 mol) and fused CH_3COONa (1 g) in HCOOH (30 ml) was heated under reflux for 3 hrs. After cooling, the reaction mixture was poured into cold H_2O and the solid product thus formed was filtered, washed with H_2O, dried and crystallized from DMF-H_2O (3 : 1) to give yellow flakes, m.p. 335C, yield 0.34 g (50%). IR: ν cm^{-1} 3020 (CH Arom.), 2950 (CH Aliph). ^{1}H NMR (CF_3COOD): δ 2.93 (s, 3 H, CH_3), 4.9 (m, 4 H, 2 CH_2-imidazoline), 7.67 (m, 3 H, Ar-H), 7.9 (m, 2 H, Ar-H), 9.67 (s, 1 H, pyridine), 10.1 (s, 1 H, triazole).
$C_{18}H_{14}N_8$ (342.4)

3.9. 2,3-Dihydro-7,10-diphenyl-12-methyl-10H-pyrazolo[4′,3′:5,6]pyrido-[3,2-e]imidazo[1,2-c]-1,2,4-triazolo[4,3-a]pyrimidine (**10b**)

A mixture of compound **9** (0.66 g, 0.002 mol) and C_6H_5COCl (0.3 g, 0.002 mol) in dry pyridine (30 ml) was heated under reflux for 2 h. The precipitate formed on hot was filtered, washed with H_2O, dried and crystallized from DMF to give yellow crystals, m.p. >360 °C, yield 0.54 g (65%). IR: ν cm^{-1} 3050 (CH Arom.), 2900 (CH Aliph). ^{1}H NMR (CF_3COOD): δ 2.93 (s, 3 H, CH_3), 4.37 (m, 2 H, CH_2-imidazoline), 4.57 (m, 2 H, CH_2-imidazoline), 7.67 (m, 10 H, Ar-H), 9.43 (s, 1H, pyridine).
$C_{24}H_{18}N_8$ (418.4)

3.10. 2,3-Dihydro-5-(3,5-dimethylpyrazol-1-yl)-10-methyl-8-phenyl-8H-pyrazolo[4′,3′:5,6]pyrido[3,2-e]imidazo[1,2-c]pyrimidine (**11**)

A mixture of compound **9** (0.66 g, 0.002 mol) and $CH_2(COCH_3)_2$ (0.2 g, 0.002 mol) in dry pyridine (15 ml) was heated under reflux for 8 h. After cooling, the solid precipitate was filtered, washed with H_2O, dried and crystallized from DMF-H_2O (1 : 1) to give yellow crystals, m.p. > 360 °C, yield 0.19 g (24%). IR: υ cm^{-1} 3020 (CH arom), 2950 (CH aliph.). ^{1}H NMR (DMSO.d_6): δ 2.67 (s, 3 H, CH_3), 2.75 (S, 3 H, CH_3), 2.93 (S, 3 H,

CH_3), 3.3 (m, 2 H, CH_2-imidazoline), 4.2 (m, 2 H, CH_2-imidazoline), 7.53 (m, 3 H, Ar-H), 8.0 (s, 1 H, pyrazole) 8.2 (m, 2 H, Ar-H), 9.1 (s, 1 H, pyridine).
$C_{22}H_{20}N_8$ (396.4)

3.11. 9-Methyl-11-phenyl-11H-pyrazolo[4′,3′: 5,6]pyrido[3,2-e]imidazo[1,2-c] [1,2,4]triazolo[4,3-a]pyrimidine-1-thiol (**12**)

A mixture of compound **9** (0.66 g, 0.002 mol) and carbon disulfide (6 ml) in dry pyridine (15 ml) was heated on a boiling water bath for 15 h. After cooling, the solid precipitate was filtered, washed with H_2O, dried and crystallized from pyridine to give yellow needles, m.p. >360 °C, yield 0.56 g (75%). IR: ν cm^{-1} 2700 (SH). ^{1}H NMR (CF_3COOD): δ 2.9 (s, 3 H, CH_3), 4.8 (m, 4 H, 2 CH_2-imidazoline), 7.67 (m, 3 H, Ar-H), 8.07 (m, 2 H, Ar-H), 9.5 (s, 1 H, pyridine).
$C_{18}H_{14}N_8S$ (374.4)

3.12. 6-Chloro-3-methyl-1-phenyl-1H-pyrazole[3,4-b]pyridine-5-carbonitrile (**14**)

A mixture of the cyanopyrazolopyridone **13** (2 g, 0.008 mol), $POCl_3$ (5 ml) and PCl_5 (2 g) was heated under reflux for 6 h. After cooling the reaction mixture was poured into H_2O and the precipitate obtained was filtered, washed with H_2O, dried and crystallized from dioxane-C_2H_5OH (1 : 1) to give pale yellow crystals, m.p. 215–217 °C, yield 1.28 g (60%). IR: ν cm^{-1} 2200 (CN). ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3 H, CH_3), 7.2–8.1 (m, 5 H, Ar-H), 8.30 (s, 1 H, pyridine).
$C_{14}H_9N_4Cl$ (268.8)

3.13. 5-(2-Imidazolin-2-yl)-6-hydrazino-3-methyl-1-phenyl-1 H-pyrazolo-[3,4-b] pyridine (**16**)

To a solution of the imidazothione **18** (3.09 g, 0.01 mol) in dry pyridine (50 ml) was added hydrazine hydrate (5 ml, 80%) and the reaction mixture was heated under reflux for 10 h. until the evolution of H_2S gas was ceased. After cooling the precipitate formed was filtered, washed with H_2O dried and purified by boiling in dioxane to give pale yellow crystals, m.p. >360 °C, yield 1.5 g (48.5%). IR: δ cm^{-1} 3420, 3220 ($NHNH_2$). ^{1}H NMR (CF_3COOD): δ 2.83 (s, 3 H, CH_3), 4.4 (s, 4 H, 2 CH_2-imidazoline), 7.73 (m, 5 H, Ar-H), 8.8 (s, 1 H, pyridine).
$C_{16}H_{17}N_7$ (307.3)

3.14. 5-(2-Imidazolin-2-yl)-3-methyl-1-phenyl-1 H-pyrazolo[3,4-b]pyridin-6(7 H)-one (**17**)

A mixture of compound **13** (5 g, 0.02 mol), ethylene diamine (15 ml) and CS_2 (1 ml) was heated on a boiling water bath for 6 h. After cooling the reaction was poured into H_2O. The solid precipitate was filtered, washed with H_2O, dried and crystallized from DMF-H_2O (1 : 1) to give yellow crystals, m.p. >360 °C, yield, 5 g (85%). IR: ν cm^{-1} 3390 (NH), 3200 (NH), 1640 (CO).^{1}H NMR (CF_3COOD): δ 2.83 (s, 3 H, CH_3), 4.27 (m, 4 H, 2 CH_2-imidazoline), 7.63 (m, 5 H, Ar-H), 9.0 (s, 1 H, pyridine).
$C_{16}H_{15}N_5O$ (293.3)

3.15. 5-(2-Imidazolin-2-yl)-3-methyl-1-phenyl-1 H-pyrazolo[3,4-b]pyridin-6(7 H)-thione (**18**)

A mixture of compound **15** (2.03 g, 0.01 mol) and P_2S_5 (0.6 g, 0.003 mol) in dry pyridine 50 ml was heated under reflux for 8 h. After cooling the reaction mixture was poured in crushed ice and acidified with CH_3COOH and left under stirring for 4 h at room temperature. The solid product was filtered, washed with H_2O, dried and crystallized from DMF-H_2O (1 : 1) to give pale yellow crystals m.p. 358 °C, yield, 2.2 g (71%). IR: ν cm^{-1} 3200 (NH).^{1}H NMR (CF_3COOD): δ 2.83 (s, 3 H, CH_3), 4.13 (m, 4 H, 2 CH_2-imidazoline), 7.66 (m, 5 H, Ar-H), 9.1 (s, 1H, pyridine).
$C_{16}H_{15}N_5S$ (309.3)

3.16. 5-(2-Imidazolin-2-yl)-3-methyl-1-phenyl-1 H-pyrazolo[4,3-e]-1,2,4-triazolo[4,3-a]pyridine (**19**)

A mixture of the hydrazine compound **18** (0.6 g: 0.002 mol) and fused CH_3COONa (1 g) and HCOOH (25 ml) was heated under reflux for 8 h. The cold reaction mixture was poured into cold H_2O and then was stirred at room temperature for 5 hrs. The solid product was crystallized from DMF-H_2O (1 : 1) to give pale yellow needles, m.p. 320 °C, yield 0.2 g (32%). IR: ν cm^{-1} 3300, 3200 (NH).^{1}H NMR (CF_3COOD): δ 2.92 (s, 3 H, CH_3), 4.03 (m, 2 H, CH_2-imidazoline), 4.73 (m, 2 H, CH_2-imidazoline), 7.3 (m, 3 H, Ar-H), 7.7 (s, 1 H, triazole), 8.07 (m, 2 H, Ar-H), 9.2 (s, 1H, pyridine).
$C_{17}H_{15}N_7$ (317.3)

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