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A Convenient Synthetic Approach to Newly Condensed Pyrazoloazines Based on Pyrazolo[3,4-*b*]pyridine+

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The reaction of 6-amino-5-cyano-3-methyl-1*H*-1-phenylpyrazolo[3,4-*b*]pyridine (**2**) and 6,7-dihydro-3-methyl-6-oxo-1*H*-1-phenylpyrazolo[3,4-*b*]pyridine-5-carbonitrile (**3**) and 5-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-1*H*-pyrazolo[4′,3′-*e*]pyridine (**12**) with different reagents have been conducted to give newly condensed pyrazoloazines.

INTRODUCTION

Pyrazolo[3,4-*b*]pyridines comprise a very interesting class of compounds because of their significant biological and pharmacological activities, acting as vasodilators, antihypertensives, hypoglycemic, anti-inflammatory, analgesic and antipyretic agents.[1-3] They have been used in treating thrombocytopenia, erythropenia[4] and pancytopenia.[5] They are also useful for the treatment of depression and obsessive compulsive disorder.[6] They have been used also as CRF antagonists[7] and as platelet aggregation inhibitors.[8] From all of the benefits mentioned above and in contiuation of our work on pyrazoloazines[9,10] we wish to present here the synthesis of some new condensed pyrazoloazines based on pyrazolo[3,4-*b*]pyridines.

RESULTS AND DISCUSSION

Cyclocondensation of 5-amino-3-methyl-1-phenylpyrazole-4-carboxaldehyde **1** with malononitrile and with ethyl cyanoacetate were reported to give 6-amino-5-cyano-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **2** and 6,7-dihydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **3** respectively.[9,11,12]

In this investigation, we found that the reaction of **1** with cyanothioacetamide in refluxing ethanolic piperidine or ethanolic triethylamine did not give the expected product, 6-amino-3-methyl-5-thiocarboxamido-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **5**, but instead compound **2** was isolated. The product isolated was assigned to be structure **2** based on compatible data of mp and mixed mp with authentic **2**.[9] The formation of **2** in this reaction can be assumed to proceed *via* the formation of the adduct **4** and subsequent loss of H_2S between amino and thioamide groups, rather than the addition of the amino group to the cyano group to produce compound **5**, as illustrated in Scheme I.

The synthetic potency of the β-enaminonitrile moiety in compound **2** was examined with some reagents in mind to synthesize condensed pyrazoloazines. The reaction of **2** with phenyl isothiocyanate, formamide, acetic anhydride, hydroxyl amine and triethyl orthoformate gave respectively the pyrazolopyridopyrimidine derivatives **6** and **7** as well as pyrazolopyridine derivatives **9**, **11** and **13**. Attempts to produce the pyrazolopyridopyridine derivative **8** by the reaction of **2** with benzoylacetonitrile in ethanolic piperidine failed (Scheme II).

In the reaction of **2** with acetic anhydride, the formation of **9** was considered, but the formation of **10** which was previously prepared[9] was disproved. Attempt of cyclization with the addition of product **11** to the amino dipyrazolopyridine derivative **12**, either by stirring in H_2SO_4 (70%) or by boiling in acetic acid was unsuccessful (Scheme III).

When product **13** was refluxed with hydrazine hydrate, 6-amino-5-imino-3-methyl-1-phenyl-1*H*-pyrazolo[3′,4′:5,6]pyrido[2,3-*b*]pyrimidine (**14**) was produced. The structure of these compounds were assigned on the basis of compatible spectroscopic and analytical data. Thus, the IR spectrum of compound **13** showed the presence of a peak at ν = 2220, indicating the presence of a CN group. The ^{1}H NMR (DMSO-d_6) revealed a triplet at δ 1.3-1.4 (3H) for ($CH_2\underline{CH_3}$) and a singlet at δ 2.6 (3H) for (CH_3) and a quartet at δ 4.4-4.6 (2H) for ($\underline{CH_2}CH_3$) and multiplet at δ 7.3-8.8 (5H) for phenyl protons and a singlet at δ 8.7 (1H) for the pyridine proton. The IR spectrum of compound **14** showed the absence of (CN) group and the presence of absorption peaks at ν = 3450-3320 cm^{-1}, indicating the presence of NH_2

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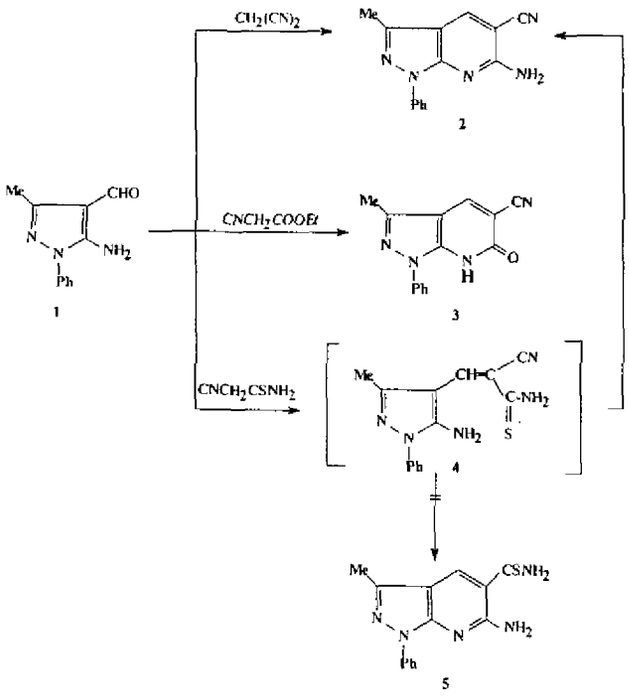
Scheme I



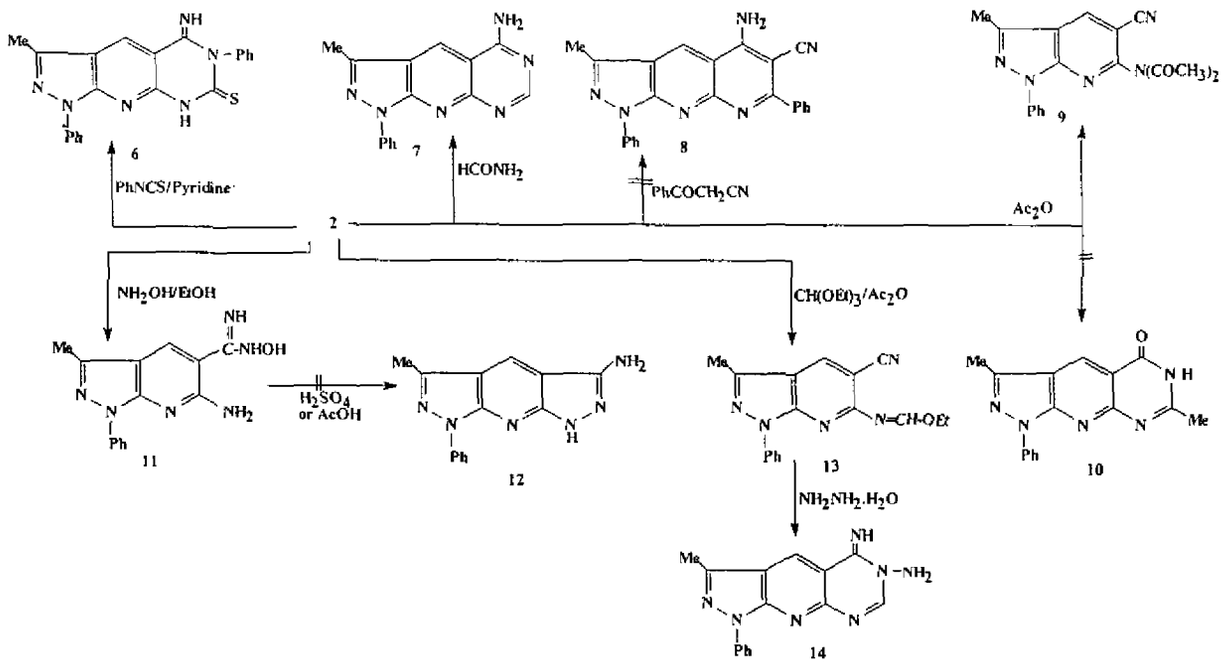
and NH. The MS spectrum revealed a signal at 291 (100%) [M$^+$] in agreement with the proposed formula $C_{15}H_{13}N_7$.

Treatment of **3** with $POCl_3/PCl_5$ or P_2S_5 in boiling pyridine furnished **15** and **16**, respectively. Treatment of **15** with thiourea in boiling ethanol did not give **16**. Alkylation of **16** with ethyl iodide gave the ethylthio derivative **17** (Scheme III).

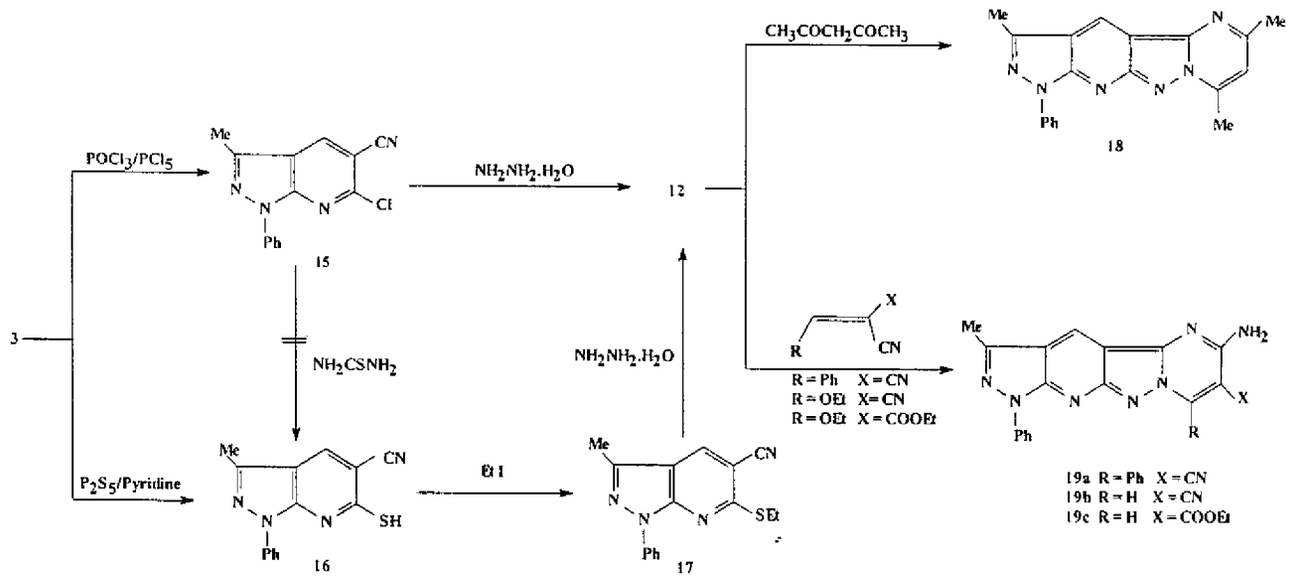
When the products **15** and **17** were subjected to the reaction with hydrazine hydrate in boiling ethanol, they yielded a cyclized product **12**, as evidence of the analytical and spectriscopic data. Thus, the IR spectrum showed absorption peaks at ν = 3400-3180 cm^{-1}, indicating the presence of NH_2 and NH groups. The ^{1}H NMR (DMSO-d_6) spectrum revealed the presence of a singlet at δ 2.60 (3H) for (CH_3) and a singlet at δ 8.7 (*1H*) for pyridine proton. Primary and secondary amino protons appeared at δ 4.80 (2H) and δ 11.25 (1H) as two singlets. Aromatic protons occurred as a multiplet at δ 7.30-8.40 (5H).

Cyclization of **12** with either β-dicarbonyl compounds or α,β-unsaturated nitriles was conducted to produce the tetracyclic compounds **18** and **19a-c**. Thus, the reaction of **12** with acetylacetone in boiling acetic acid gave 3,6,8-trimethyl-1*H*-1-phenylpyrazolo[4″,3″:5′,6′]pyrido[3′,2′:4,5] pyrazolo[2,3-*a*]pyrimidine **18**. Compound **12** reacted with benzylidenemalononitrile, ethoxymethylenemalononitrile or ethyl (ethoxymethylene)cyanoacetate in refluxing ethanolic piperidine to give the tetracyclic compounds **19a-**

Scheme II



Scheme III



c (Scheme III). The structures of all of these synthesized compounds were confirmed on the basis of their elemental analyses, IR and ^{1}H NMR spectral data. Thus, the IR spectrum of compound **18** showed no signals for NH_2 and NH groups. Its ^{1}H NMR spectrum (CF_3COOD) revealed the presence of a singlet at δ 2.8 (3H, CH_3) and a singlet at δ 2.9 (6H, $2CH_3$). Compound **19c**, for example, showed the IR spectrum absorption peaks at ν 3300-3180 cm^{-1}, indicating the presence of a NH_2 group. The ^{1}H NMR spectrum (CF_3COOD) showed signals at δ 1.4-1.6 (3H, t, $CH_2\underline{CH_3}$), δ 2.9 (3H, s, CH_3), δ 4.5-4.7 (2H, q, $\underline{CH_2}CH_3$), δ 8.3 (1H, s, for pyridine proton) and at δ 7.7-8.0 (5H, m, Ar-H).

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp II melting points apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP3-100 Spectrophotometer using the KBr Wafer technique (ν_{max} in cm^{-1}). The ^{1}H NMR spectra were recorded on a 90 MHz Varian EM-390 NMR spectrophotometer in suitable deuterated solvents using TMS as an internal reference (chemical shifts in δ values). The elemental analyses were carried out on a Perkin-Elmer 240 C elemental analyzer and MS spectra on a Finnigan Mat SSQ7000 spectrometer. The characterization of all newly synthesised compounds are given in Table 1. Satisfactory elemental analyses (C,H,N) were obtained for all compounds.

Compounds **1**, **2** and **3** were prepared according to methods described in the literature.[9-12]

1,6-Diphenyl-5-imino-3-methyl-7-thioxo-1*H*-pyrazolo-[3,4:6,5]pyrido[2,3-*e*]pyrimidine (6)

A mixture of compound **2** (1.0 g; 4 mmol) and excess phenyl isothiocyanate (0.4 mL) in pyridine (25 mL) was heated under reflux for 50 h. After cooling, the reaction mixture was poured into cold water and the solid product obtained was crystallized from dioxane-water (3:1) to give small yellow needles (0.43 g, 28%).

5-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4:6,5]-pyrido[2,3-*b*]pyrimidine (7)

A mixture of compound **2** (1.0 g; 4 mmol) and formamide (15 mL) was heated under reflux for 2 hr. After cooling, the reaction mixture was poured into water and the solution was salted with sodium chloride and stirred at room temperature for 3 hr. The solid product obtained by filtration was washed with water and crystallized from dioxane-water (5:1) to give yellow small crystals (0.46 g, 42%).

5-Cyano-6-diacetylamino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (9)

A mixture of compound **2** (1.0 g; 4 mmol), acetic anhydride (10 mL) and pyridine (5 mL) was heated on a water bath for 8 h. After cooling, the reaction mixture was poured into water and left overnight with stirring and the solid product obtained was washed with water, dried and crystallized from dioxane-water (1:1) to give buff flakes (0.82 g, 62%).

Table 1. The Characterization of the Newly Synthesized Compounds

Compd. No.	mp °C (% Yield)	Mol. Formula (M. Wt)	IR /cm^{-1}	^{1}H NMR/δ	MS *m/z* (%)
6	335 (28)	$C_{21}H_{16}N_6S$ (384.4)	3370 (NH)	(CF_3COOD): 2.85 (s, 3H, CH_3); 7.6-7.8 (m, 10H, Ar-H); 9.1 (s, 1H, pyridin-H)	384 (14)
7	340 (42)	$C_{15}H_{12}N_6$ (276.3)	3400-3300 (NH_2)	(CF_3COOD): 2.9 (s, 3H, CH_3); 7.5-7.7 (m, 5H, Ar-H); 9.1 (s, 1H, pyridin-H)	276 (33)
9	175 (62)	$C_{18}H_{15}N_5O_2$ (333.3)	2200 (CN) 1710, 1690 (CO)	(DMSO-d_6): 2.3 (s, 3H, CH_3); 2.4 (s, $COCH_3$), 2.5 (s, $COCH_3$), 7.5-8.3 (*m*, 5H, Ar-H); 9.05 (*s*, 1H, pyridin-H)	
11	248 (58)	$C_{14}H_{14}N_6O$ (282.3)	3400 (OH) 3300-3200 (NH_2+2NH)	(DMSO-d_6): 2.5 (s, 3H, CH_3); 6.0 (s, 2H, NH_2), 7.5-7.7 (m, 5H, Ar-H), 8.3 (s, 2H, NH), 8.3 (s, 1H, pyridin-H), 9.8 (s, 1H, OH)	282 (100)
12	220 (61)	$C_{14}H_{12}N_6$ (264.3)	3400-3180 (NH_2+NH)	(DMSO-d_6): 2.6 (s, 3H, CH_3); 4.8 (s, 2H, NH_2), 7.3-8.4 (m, 5H, Ar-H), 8.7 (s, 1H, pyridine-H), 11.2 (s, 1H, NH)	
13	162 (65)	$C_{17}H_{15}N_5O$ (305.3)	2220 (CN)	(DMSO-d_6): 1.3-1.4 (t, 3H, CH_3); 2.6 (s, 3H, CH_3); 4.4-4.6 (q, 2H, CH_2), 7.3-8.4 (m, 5H, Ar-H), 8.7 (s, 1H, pyridin-H)	
14	>360 (52)	$C_{15}H_{13}N_7$ (291.3)	3450-3320 (NH+NH_2)	insol. in most deuterated solvents	291 (100)
15	215 (58)	$C_{14}H_9ClN_4$ (268.8)	2200 (CN)	($CDCl_3$): 2.55 (s, 3H, CH_3), 7.2-8.1 (m, 5H, Ar-H), 8.3 (s, 1H, pyrdin-H)	268 (93)
16	260 (42)	$C_{14}H_{10}N_4S$ (266.3)	2230 (CN)	(DMSO-d_6): 2.55 (s, 3H, CH_3), 7.2-8.2 (m, 5H, Ar-H), 9.25 (s, 1H, pyridine-H), 11.8 (s, 1H, *SH*)	
17	180 (53)	$C_{16}H_{14}N_4S$ (294.3)	2200 (CN)	($CDCl_3$): 1.4-1.6 (t, 3H, CH_3), 2.5 (s, 3H, CH_3), 4.5-4.7 (q, 2H, CH_2), 7.3-8.3 (m, 5H, Ar-H), 8.2 (s, 1H, pyridin-H)	
18	320 (77)	$C_{19}H_{16}N_6$ (328.3)	3000 (arom. CH) 2950 (aliph. CH)	(CF_3COOD): 2.8 (s, 3H, CH_3), 2.9 (s, 6H, $2CH_3$), 6.7 (s, 1H, pyrimidin-H), 7.8 (s, 5H, Ar-H), 8.7 (s, 1H, pyridin-H)	328 (100)
19a	>360 (58)	$C_{24}H_{16}N_8$ (416.4)	3400-3280 (NH_2), 2210 (*CN*)	(CF_3COOD): 2.95 (s, 3H, CH_3), 7.7-8.0 (m, 10H, Ar-H), 8.2 (s, *1H, pyridin-H*)	
19b	>360 (52)	$C_{18}H_{12}N_8$ (340.3)	3400-3250 (NH_2); 2210 (CN)	(CF_3COOD): 2.95 (s, 3H, CH_3), 7.7-8.0 (m, 5H, Ar-H), 8.2 (s, 1H, pyridin-H)	
19c	>360 (38)	$C_{20}H_{17}N_7O_2$ (387.3)	3300-3180 (NH_2)	(CF_3COOD): 1.4-1.6 (t, 3H, CH_3), 2.9 (s, 3H, CH_3), 4.5-4.7 (q, 2H, CH_2), 7.7-8.0 (m, 5H, Ar-H), 8.3 (s, 1H, pyridin-H)	

5-Amidoximo-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (11)

A mixture of compound **2** (1.0 g; 4 mmol), hydroxylamine hydrochloride (0.28 g; 4 mmol) and an excess of sodium acetate (1.0 g) in ethanol (30 mL) was heated on a water bath for 6 h. After cooling, the reaction mixture was

poured into water. The solid product obtained was washed with water, dried and crystallized from ethanol to give yellow flakes (0.65 g, 58%).

5-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-1*H*-pyrazolo[3′,4′-*e*]pyridine (12)

A mixture of compound **15** (2.68 g; 10 mmol) and hydrazine hydrate (80%, 1.25 mL, 20 mmol) in ethanol (30 mL) was heated on a water bath for 6 h. After cooling, the reaction mixture was poured into water and the solid product obtained was washed with water, dried and crystallized from diluted ethanol to give yellow crystals (1.61 g, 61%).

5-Cyano-6-ethoxymethyleneamino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (13)

A mixture of compound **2** (1.0 g; 4 mmol), triethyl orthoformate (10 mL) and a few drops of acetic anhydride was heated under reflux for 6 h. The solid product obtained was crystallized from ethanol to give pale yellow needles (0.79 g, 65%).

6-Amino-5-imino-3-methyl-1-phenyl-1*H*-pyrazolo-[3′,4′:5,6]pyrido[2,3-*b*]pyrimidine (14)

A mixture of compound **13** (0.61 g; 2 mmol) and hydrazine hydrate (80%, 0.25 mL, 4 mmol) in ethanol (50 mL) was heated under reflux for 4 h. The solid product was crystallized from dioxane to give yellow crystals (0.3 g, 52%).

6-Chloro-5-cyano-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (15)

A mixture of compound **3** (2.0 g; 8 mmol), $POCl_3$ (3 mL) and PCl_5 (2 g) was heated under reflux for 6 h. After cooling, the reaction mixture was poured into water and the solid product obtained was washed with water and crystallized from ethanol-dioxane (1:1) to give pale yellow crystals (1.3 g, 58%).

5-Cyano-3-methyl-6-mercapto-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (16)

A mixture of compound **3** (2.5 g; 10 mmol) and P_2S_5 (0.88 g, 2 mmol) in pyridine (30 mL) was heated under reflux for 8 h. After cooling, the reaction mixture was poured into water acidified with HCl and stirred at room temerature for 6 h. The solid product obtained was crystallized from dioxane to give yellow crystals (1.12 g, 42%).

5-Cyano-6-ethylthio-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (17)

A mixture of compound **16** (1.06 g; 4 mmol), ethyl iodide (3.74 g, 4 mmol) and sodium acetate (0.5 g) in ethanol (30 mL) was heated under reflux for 3 h. The solid product obtained was crystallized from methanol to give yellow crystals (0.62 g, 53%).

3,6,8-Trimethyl-1*H*-phenylpyrazolo[4″,3″:5′,6′]-pyrido[3′,2′:4,5]pyrazolo[2,3-*a*]pyrimidine (18)

A mixture of compound **12** (1.04 g; 4 mmol) and acetylacetone (0.4 g, 4 mmol) in acetic acid (20 mL) was heated under reflux for 2 h. The solid product was crystallized from dioxane-DMF (3:1) to give yellow needles (1.0 g, 77%).

Preparation of Compounds 19a-c: General Procedure

A mixture of compound **12** (1.04 g; 4 mmol) and benzylidinemalononitrile or (ethoxymethylene)malononitrile or ethyl (ethoxymethylene)cyanoacetate (4 mmol) in ethanol (30 mL) containing a few drops of piperidine was heated under reflux for 2-10 hr. After cooling, the reaction mixture was poured into water, neutralized with diluted HCl and the solid product collected was crystallized as shown below.

6-Amino-1,8-diphenyl-3-methyl-1*H*-pyrazolo-[4″,3″:5′,6′]pyrido[3′,2′:4,5]pyrazolo[2,3-*a*]pyrimidine-7-carbonitrile (19a)

Fine orange needles from dionane-water (2:1) (0.96 g, 58%).

8-Amino-1-phenyl-3-methyl-1*H*-pyrazolo-[4″,3″:5′,6′]pyrido[3′,2′:4,5]pyrazolo[2,3-*a*]pyrimidine-7-carbonitrile (19b)

Yellow needles from dionane-water (3:1) (0.7 g, 52%).

Ethyl 8-Amino-3-methyl-1-phenyl-1*H*-pyrazolo-[4″,3″:5′,6′]pyrido[3′,2′:4,5]pyrazolo[2,3-*a*]pyrimidine-7-carboxylate (19c)

Yellow needles from dioxane-water (1:1) (0.58 g, 38%).

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Key Words

Pyrazolo[3,4-*b*]pyridines; Pyrazoloazines; Pyrazolopyridopyridines; Pyrazolopyrido; Pyrimidines.

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