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An efficient synthesis and characterization of some novel pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives

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ABSTRACT

A simple and efficient approach towards single step synthesis of pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives has been developed by condensation reaction of ethyl ester of 5-amino-1-substituted-1*H*-pyrazole-4-carboxylate with different aromatic nitriles under acidic conditions. All the newly synthesized compounds were characterized by spectroscopic techniques (IR, NMR and Mass spectra) and elemental analysis.

Keywords: Single step synthesis, *ortho* amino ester of pyrazole, aromatic nitriles, pyrazolo[3,4-*d*]pyrimidine derivatives.

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INTRODUCTION

The heterocyclic fusion of pyrazole and pyrimidine ring resulted in formation of pyrazolopyrimidine, the structural analogues of biogenic purine, which made them a prime target for scientific research. Indisputably, pyrazolopyrimidine derivatives have high significance in the field of medical sciences with wide range of biological activities like antimicrobial,[1,2] antitumor,[2] antibacterial,[3] adenosine receptor antagonist,[4] non-narcotic analgesic,[5] antinociceptive,[6] anti-inflammatory,[5,6] antiviral[7] and leishmanicidal.[8] It has also been well established that these heterocyclic compounds are effective inhibitors of xanthine oxidase,[9] GSK-3[10] and *Mycobacterium tuberculosis*.[11]

Various synthetic approaches are well documented for the synthesis of pyrazolo[3,4-*d*]pyrimidines from *ortho* amino nitriles of pyrazole.[9,12-14] However, the transformation of 5-amino-1-substituted-1*H*-pyrazole-4-carbonitrile to pyrazolo[3,4-*d*]pyrimidine requires two steps and suffers from several disadvantages such as vigorous reaction condition, long reaction times and low yields.[15,16] Recently, Bakavoli *et al*. [3] reported single step synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives by iodocyclization of 5-amino-1-(2,4-dinitrophenyl)-1*H*-4-pyrazolcarboxamides with aromatic aldehydes.

The literature survey also showed that few attempts were made to synthesize heterofused pyrazolopyrimidine ring system from *ortho* amino esters of pyrazole. This observation motivated us to develop single step and efficient synthesis of pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives.

MATERIALS AND METHOD

All reagents and solvents used were of LR grade, obtained from SD fine chemicals (Mumbai, India) and were used without additional purification. Precoated silica gel F_{254} plates (Merck, India) were used for analytical and preparative TLC. Iodine chamber and UV lamp (λ = 254 nm) were used for visualization of the spots. Melting points were determined in an open capillary tube on Chemline CL726 melting point apparatus and were uncorrected. IR spectra (ν_{max}, cm^{-1}) were recorded in KBr pellets on Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR (δ, ppm) spectra were recorded in DMSO-d_6 using TMS as internal standard on Bruker advance III NMR spectrophotometer at 400 MHz. Mass spectra were determined on Shimadzu GC-MS QP 2010 mass spectrometer. Elemental analysis was performed with Elementar Vario EL III analyzer for C, H, N, and the results were found within ±0.4% of the calculated value. The starting material 3-

nitro-4-hydrazinopyridine and ethyl-2-cyano-3-ethoxy acrylate were synthesized according to reported method.[17,18]

General synthetic procedure for preparation of 2a and 2b:

To a solution of ethyl-2-cyano-3-ethoxyacrylate (30 mM) and piperidine (0.3 mL) in dioxane (75 mL), 3-nitro-4-hydrazinopyridine 1a or *p*-methyl phenyl hydrazine 1b (30 mM) was added in small lots over period of 1 h, under vigorous stirring. The stirring was continued for 2-3 h and then reaction mixture was kept in refrigerator overnight, the formed solid was filtered and recrystallized from suitable solvent to afford compound 2a and 2b respectively.

- *Ethyl 5-amino-1-(3-nitropyridin-4-yl)-1H-pyrazole-4-carboxylate* **(2a):**

Yield: 61% (Dioxane); m.p.: 156-157°C [Reported[19]: Yield: 40%; m.p.: 158-159°C]; R_f: 0.55 (Toluene : Ethyl acetate (7:3)); IR (KBr, *v*, cm^{-1}): 3312, 3195, 2968, 2912, 1689; ^1H NMR ($CDCl_3$, δ): 1.39 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 5.44 (s, 2H, NH_2), 7.62 (d, 1H, CH), 7.82 (s, 1H, CH), 8.87 (d, 1H, CH), 9.21 (s, 1H, CH); MS: *m/z* 277 (M^+); Anal. Calcd. for $C_{11}H_{11}N_5O_4$: C, 47.66; H, 4.00; N, 25.26. Found: C, 47.73; H, 4.06; N, 25.19.

- *Ethyl 5-amino-1-p-tolyl-1H-pyrazole-4-carboxylate* **(2b):**

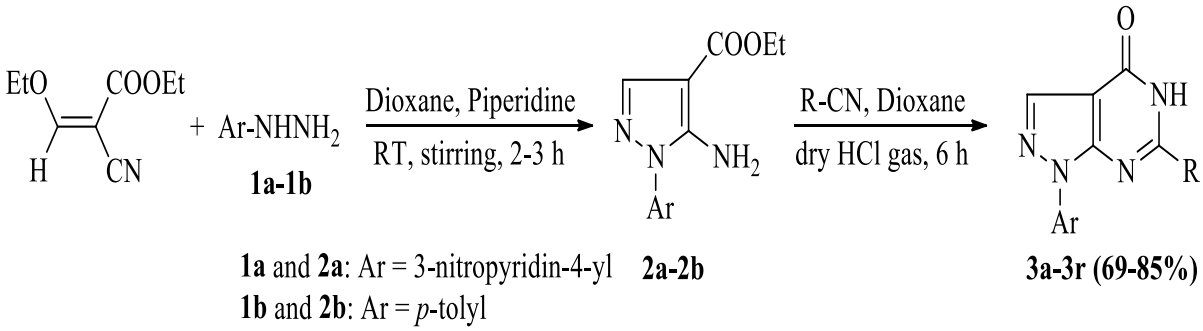
Yield: 84% (Ethanol); m.p.: 144-146°C; R_f: 0.63 (Toluene : Ethyl acetate (7:3)); IR (KBr, *v*, cm^{-1}): 3334, 3190, 2969, 2900, 1690; ^1H NMR ($CDCl_3$, δ): 1.38 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.22 (q, 2H, CH_2), 5.44 (s, 2H, NH_2), 7.28-7.40 (m, 4H, aro. CH), 7.81 (s, 1H, CH); MS: *m/z* 245 (M^+); Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.53; H, 6.18; N, 17.08.

General synthetic procedure for preparation of pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives (3a-3r)

Ortho amino ester of pyrazole 2a or 2b (10 mM) and various aromatic nitriles (15 mM) in dioxane (15 mL) were taken in a conical flask and a stream of dry hydrogen chloride gas was passed through the mixture for 6 h. The reaction mixture was poured into a beaker containing crushed ice and basified with 10% ammonium hydroxide solution. The solid thus obtained was filtered, dried and recrystallized from ethanol to give the target compounds in good to excellent yields.

RESULTS AND DISCUSSION

Compounds ethyl 5-amino-1-substituted-1*H*-pyrazole-4-carboxylate (2a and 2b) and a series of 1,6-substituted-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives (3a-3r) were prepared in good yields using the appropriate synthetic procedures as per the scheme 1.



Scheme 1 Synthetic route of compounds **3a-3r**

Earlier, Ciciani *et al.*[19] reported the synthesis of compound 2a having just 40% yield. We have developed a new method for the synthesis of compounds 2a and 2b in good yields by reacting ethyl-2-cyano-3-ethoxyacrylate with 3-nitro-4-hydrazinopyridine or *p*-methyl phenyl hydrazine respectively. The reactants were stirred in dioxane in presence of piperidine as a catalyst. Upon cooling, precipitated solid was purified by recrystallisation.

The structures of these compounds were confirmed from their spectral and micro analytical data. The IR spectrum of compound 2a showed asymmetric and symmetric stretching of primary amino group (3312 and 3195 cm^{-1}) and presence of carbonyl group (1689 cm^{-1}). The ^1H NMR of 2a showed triplet and quartet at δ 1.39 (3H) and δ 4.23 (2H) indicating the presence of an ethyl group of the ester, singlet at δ 5.44 (2H) indicating the presence of NH_2 group and singlet at δ 7.82 (1H) which corresponds to the pyrazole ring proton. The three aromatic protons of the 3-nitro-pyridin-4-yl ring were appeared in the range of 7.62-9.21 δ, ppm. In the mass spectrum of compound 2a, the molecular ion peak (M^+) appeared at m/z 277, which was identical with its molecular formula.

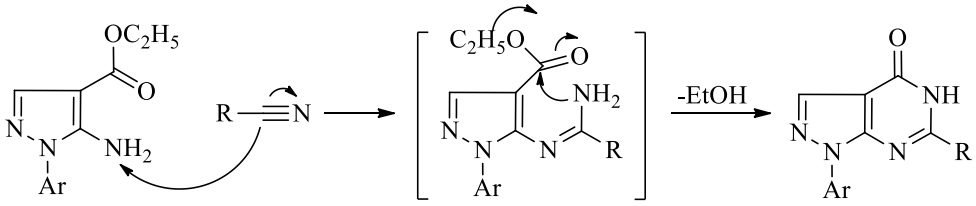
Dave *et al.*[20] reported the reaction of various nitriles with *ortho* amino carbonyl compounds in acidic conditions to yield the corresponding condensed pyrimidines in fair to good yields. The condensation reaction of compounds 2a and 2b with various aromatic nitriles in the presence of dry hydrochloric acid in dioxane gave 1,6-substituted-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives (3a-3r) in good to excellent yields. The physicochemical data and elemental analysis of all the newly synthesized compounds are summarized in Table 1.

Table 1 Physicochemical data and elemental analysis of synthesized compounds (3a-3r)

Compds.	R	Ar	%Yield[#]	Melting Point(°C)	R_f[*]	Elemental analysis Found (Calculated)		
						C	H	N
3a	C_6H_5-	*3-nitropyridin-4-yl*	77	254-255	0.41	57.53 (57.49)	3.08 (3.02)	25.15 (25.14)
3b	4-MeC_6H_4-	*3-nitropyridin-4-yl*	70	>300	0.47	58.58 (58.62)	3.38 (3.47)	24.17 (24.13)
3c	4-OMeC_6H_4-	*3-nitropyridin-4-yl*	70	>300	0.40	56.08 (56.05)	3.39 (3.32)	23.14 (23.07)
3d	4-ClC_6H_4-	*3-nitropyridin-4-yl*	85	>300	0.48	52.21 (52.12)	2.51 (2.46)	22.72 (22.79)
3e	4-BrC_6H_4-	*3-nitropyridin-4-yl*	73	294-296	0.50	46.48 (46.51)	2.13 (2.20)	20.30 (20.34)
3f	4-$NO_2C_6H_4$-	*3-nitropyridin-4-yl*	85	>300	0.40	50.60 (50.67)	2.38 (2.39)	25.90 (25.85)
3g	3-$NO_2C_6H_4$-	*3-nitropyridin-4-yl*	80	>300	0.40	50.62 (50.67)	2.43 (2.39)	25.82 (25.85)
3h	4-OHC_6H_4-	*3-nitropyridin-4-yl*	72	>300	0.37	54.80 (54.86)	2.78 (2.88)	23.96 (23.99)
3i	3-OHC_6H_4-	*3-nitropyridin-4-yl*	69	>300	0.37	54.92 (54.86)	2.84 (2.88)	24.03 (23.99)
3j	C_6H_5-	*p-tolyl*	75	244-246	0.46	71.53 (71.51)	4.80 (4.67)	18.43 (18.53)
3k	4-MeC_6H_4-	*p-tolyl*	71	>300	0.52	72.18 (72.13)	5.13 (5.10)	17.68 (17.71)
3l	4-OMeC_6H_4-	*p-tolyl*	72	>300	0.45	68.75 (68.66)	4.92 (4.85)	16.78 (16.86)
3m	4-ClC_6H_4-	*p-tolyl*	83	>300	0.53	64.38 (64.19)	4.01 (3.89)	16.49 (16.64)
3n	4-BrC_6H_4-	*p-tolyl*	71	289-291	0.55	56.79 (56.71)	3.44 (3.37)	14.80 (14.70)
3o	4-$NO_2C_6H_4$-	*p-tolyl*	84	>300	0.45	62.33 (62.24)	3.68 (3.77)	20.10 (20.16)
3p	3-$NO_2C_6H_4$-	*p-tolyl*	78	>300	0.45	62.36 (62.24)	3.63 (3.77)	20.22 (20.16)
3q	4-OHC_6H_4-	*p-tolyl*	76	>300	0.42	67.02 (67.10)	3.91 (3.97)	18.37 (18.41)
3r	3-OHC_6H_4-	*p-tolyl*	69	>300	0.42	66.98 (67.10)	3.89 (3.97)	18.48 (18.41)

[#] Yield refers to pure isolated product; [*] Mobile Phase = Toluene : Ethyl acetate (7:3)

This facile, one-pot reaction presumably proceeds via the amidine intermediate which undergoes intramolecular cyclization with the elimination of ethanol to produce targeted compounds**.** The reaction mechanism is depicted in scheme 2.



Scheme 2 Reaction mechanism for synthesis of pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one

The structures of these compounds were confirmed from their spectral and elemental analysis. The IR, ^{1}H NMR and mass spectra supported the structure of various synthesized pyrazolopyrimidines are recorded in Table 2. The disappearance of two peaks of primary amino group and appearance of secondary amino peak (3184 cm^{-1}) and shifting of carbonyl peak to 1649 cm^{-1} indicated the cyclization of *ortho* amino ester of pyrazole. The ^{1}H NMR spectrum of compound 3j showed a singlet for NH proton at 12.45 δ ppm. The 5 aromatic protons of phenyl ring appear as a multiplet between 7.50 to 7.62 δ ppm. On the other hand, 4 aromatic protons of tolyl ring appear as a multiplet at 7.26-7.40 δ ppm, while methyl group of the tolyl ring gave a singlet at 2.36 δ ppm. The molecular ion peak of compound 3j was observed at m/z 302 (M^{+}), which was in accordance with its molecular formula. All the elemental analysis data of synthesized compounds were in accordance with the suggested structures.

Table 2 Spectral data of synthesized compounds (3a-3r)

Compds.	IR (KBr, *v*, cm^{-1})	^1H NMR (DMSO-d_6, δ, ppm)	MF (MW) Mass (m/z)
3a	3184, 3071, 2969, 2910, 1649, 1578	7.52-7.64 (m, 5H, aro. CH), 7.62 (d, 1H, CH), 7.82 (s, 1H, CH), 8.87 (d, 1H, CH), 9.21 (s, 1H, CH), 12.44 (s, 1H, NH)	$C_{16}H_{10}N_6O$ (334.29) 334 (M^+)
3b	3191, 3073, 2968, 2910, 1651, 1578	2.35 (s, 3H, CH_3), 7.22 (d, 2H, aro. CH), 7.42 (d, 2H, aro. CH), 7.63 (d, 1H, CH), 7.82 (s, 1H, CH), 8.87 (d, 1H, CH), 9.21 (s, 1H, CH), 12.44 (s, 1H, NH)	$C_{17}H_{12}N_6O_3$ (348.32) 348 (M^+)
3c	3189, 3071, 2966, 2908, 1649, 1576	3.84 (s, 3H, CH_3), 6.95 (d, 2H, aro. CH), 7.23 (d, 2H, aro. CH), 7.63 (d, 1H, CH), 7.83 (s, 1H, CH), 8.88 (d, 1H, CH), 9.22 (s, 1H, CH), 12.45 (s, 1H, NH)	$C_{17}H_{12}N_6O_4$ (364.32) 364 (M^+)
3d	3190, 3071, 2967, 2910, 1650, 1577	7.62 (d, 1H, CH), 7.67 (d, 2H, aro. CH), 7.83 (s, 1H, CH), 8.15 (d, 2H, aro. CH), 8.88 (d, 1H, CH), 9.22 (s, 1H, CH), 12.46 (s, 1H, NH)	$C_{16}H_9ClN_6O_3$ (368.74) 368 (M^+), 370(M^{+2})
3e	3190, 3070, 2969, 2912, 1650, 1579	7.63 (d, 1H, CH), 7.69 (d, 2H, aro. CH), 7.83 (s, 1H, CH), 8.20 (d, 2H, aro. CH), 8.88 (d, 1H, CH), 9.22 (s, 1H, CH), 12.45 (s, 1H, NH)	$C_{16}H_9BrN_6O_3$ (413.19) 412 (M^+), 414 (M^{+2})
3f	3192, 3071, 2970, 2913, 1648, 1576	7.63 (d, 1H, CH), 7.83 (s, 1H, CH), 7.89 (d, 2H, aro. CH), 8.35 (d, 2H, aro. CH), 8.88 (d, 1H, CH), 9.22 (s, 1H, CH), 12.46 (s, 1H, NH)	$C_{16}H_9N_7O_5$ (379.29) 379 (M^+)
3g	3189, 3070, 2968, 2909, 1647, 1574	7.63 (d, 1H, CH), 7.83 (s, 1H, CH), 7.98 (t, 1H, aro. CH), 8.20 (d, 2H, aro. CH), 8.45 (s, 1H, aro. CH), 8.88 (d, 1H, CH), 9.22 (s, 1H, CH), 12.45 (s, 1H, NH)	$C_{16}H_9N_7O_5$ (379.29) 379 (M^+)
3h	3190, 3070, 2967, 2908, 1650, 1577	6.87 (d, 2H, aro. CH), 7.38 (d, 2H, aro. CH), 7.63 (d, 1H, CH), 7.83 (s, 1H, CH), 8.88 (d, 1H, CH), 9.22 (s, 1H, CH), 9.86 (s, 1H, OH), 12.44 (s, 1H, NH)	$C_{16}H_{10}N_6O_4$ (350.29) 350 (M^+)
3i	3191, 3072, 2968, 2910, 1650, 1579	7.10-7.22 (m, 4H, aro. CH), 7.63 (d, 1H, CH), 7.83 (s, 1H, CH), 8.88 (d, 1H, CH), 9.22 (s, 1H, CH), 9.86 (s, 1H, OH), 12.45 (s, 1H, NH)	$C_{16}H_{10}N_6O_4$ (350.29) 350 (M^+)
3j	3190, 3071, 2969, 2911, 1652, 1579	2.36 (s, 3H, CH_3), 7.26-7.40 (m, 4H, aro. CH), 7.50-7.62 (m, 5H, aro. CH), 7.83 (s, 1H, CH), 12.45 (s, 1H, NH)	$C_{18}H_{14}N_4O$ (302.33) 302 (M^+)
3k	3194, 3075, 2971, 2913, 1653, 1580	2.35 (s, 6H, CH_3), 7.25-7.40 (m, 8H, aro. CH), 7.84 (s, 1H, CH), 12.46 (s, 1H, NH)	$C_{19}H_{16}N_4O$ (316.36) 316 (M^+)
3l	3192, 3073, 2968, 2912, 1651, 1580	2.35 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 6.95 (d, 2H, aro. CH), 7.23-7.39 (m, 6H, aro. CH), 7.84 (s, 1H, CH), 12.46 (s, 1H, NH)	$C_{19}H_{16}N_4O_2$ (332.36)

			332 (M^{+})
3m	3196, 3078, 2973, 2915, 1656, 1583	2.35 (s, 3H, CH_3), 7.25-7.41 (m, 4H, aro. CH), 7.67 (d, 2H, aro. CH), 7.84 (s, 1H, CH), 8.15 (d, 2H, aro. CH), 12.46 (s, 1H, NH)	$C_{18}H_{13}ClN_4O$ (336.78) 336 (M^{+}), 338 (M^{+2})
3n	3194, 3076, 2971, 2913, 1654, 1581	2.35 (s, 3H, CH_3), 7.26-7.40 (m, 4H, aro. CH), 7.69 (d, 2H, aro. CH), 7.83 (s, 1H, CH), 8.20 (d, 2H, aro. CH), 12.45 (s, 1H, NH)	$C_{18}H_{13}BrN_4O$ (381.23) 380 (M^{+}), 382 (M^{+2})
3o	3188, 3070, 2965, 2907, 1648, 1575	2.35 (s, 3H, CH_3), 7.27-7.40 (m, 4H, aro. CH), 7.83 (s, 1H, CH), 7.89 (d, 2H, aro. CH), 8.35 (d, 2H, aro. CH), 12.46 (s, 1H, NH)	$C_{18}H_{13}N_5O_3$ (347.33) 347 (M^{+})
3p	3190, 3073, 2968, 2910, 1651, 1578	2.35 (s, 3H, CH_3), 7.26-7.40 (m, 4H, aro. CH), 7.83 (s, 1H, CH), 7.98 (t, 1H, aro. CH), 8.20 (d, 2H, aro. CH), 8.45 (s, 1H, aro. CH), 12.46 (s, 1H, NH)	$C_{18}H_{13}N_5O_3$ (347.33) 347 (M^{+})
3q	3190, 3071, 2966, 2909, 1650, 1576	2.35 (s, 3H, CH_3), 6.87 (d, 2H, aro. CH), 7.22-7.42 (m, 6H, aro. CH), 7.83 (s, 1H, CH), 9.86 (s, 1H, OH), 12.44 (s, 1H, NH)	$C_{17}H_{12}N_4O_2$ (304.30) 304 (M^{+})
3r	3191, 3071, 2965, 2905, 1648, 1574	2.34 (s, 3H, CH_3), 7.10-7.22 (m, 4H, aro. CH), 7.27-7.40 (m, 4H, aro. CH), 7.83 (s, 1H, CH), 9.86 (s, 1H, OH), 12.46 (s, 1H, NH)	$C_{17}H_{12}N_4O_2$ (304.30) 304 (M^{+})

CONCLUSION

A new and efficient method for the synthesis of compounds 2a and 2b in good yields by reacting ethyl-2-cyano-3-ethoxyacrylate with 3-nitro-4-hydrazinopyridine or *p*-methyl phenyl hydrazine respectively in dioxane using piperidine as a catalyst has been developed which give good yields. A series of 1,6-substituted-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H)*-one derivatives were prepared in quantitative yield by simple and efficient conventional method.

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