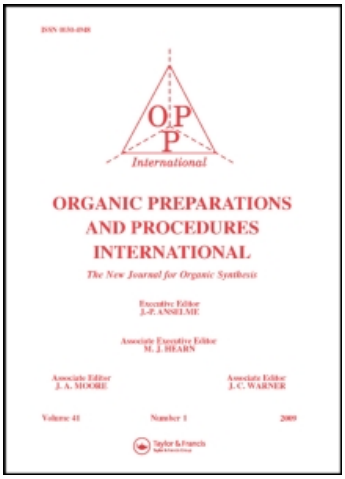

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A FACILE SYNTHESIS OF 6-ARn-l-METHYL-3-n-PROPn-6,7-DIHYDRO-1H-PYRAZOLO[4,3-d]PYRIMIDIN-7-OMES

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A FACILE SYNTHESIS OF 6-ARYL-1-METHYL-3-*n*-PROPYL-6,7-DIHYDRO-1*H*-PYRAZOLO[4,3-*d*]PYRIMIDIN-7-ONES

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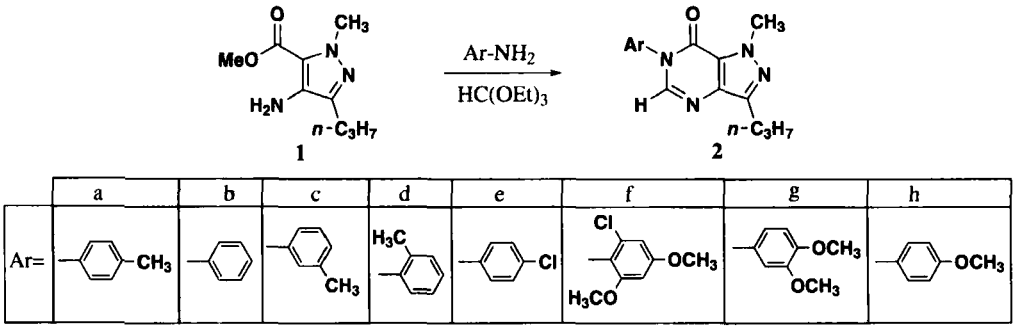
Pyrazolo[4,3-*d*]pyrimidines have attracted interest in view of their immense pharmacological importance. As structural analogues of purines, they have shown adenosine receptor antagonist activty[1] and some were found to act as vasodilators.[2] As structural constituents of formycin A and B, they exhibited promising antibacterial activity.[3,4] They also have therapeutic value in the treatment of various cardiovascular disorders.[5,6] Earlier, Baraldi and co-workers reported the synthesis of ribofuranosyl pyrazolo[4,3-*d*]pyrimidine nucleosides containing 3-methyl-6-substituted-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one as the aglycon moiety.[7] These compounds are N-nucleoside analogues of formycin B and were found to have antiviral activity.

A synthesis of the title compounds was envisaged from the condensation of methyl 4-amino-1-methyl-3-*n*-propyl pyrazole-5-carboxylate (**1**) with triethyl orthoformate (TEOF) in the presence of aromatic amines. The required amino ester **1** was accessed from 1-methyl-4-nitro-3-*n*-propyl pyrazole-5-carboxylic acid[8] through a two-step synthetic sequence. An equimolar mixture of **1** and *p*-toluidine in combination with slight excess of TEOF was refluxed in dry xylene for 6 h. Dilution of the reaction mixture with n-hexane yielded 1-methyl-6-(4-methylphenyl)-3-*n*-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (**2a**), characterized based on its IR, Mass, ^{1}H and ^{13}C NMR spectral data and elemental analysis. To test its generality, this method was extended to seven other aromatic amines and in all the cases corresponding pyrazolo[4,3-*d*]pyrimidines (**2b-h**) were isolated in good yields.



Scheme 1

Thus, a facile one-pot method is provided for the biologically important pyrazolo[4,3-*d*]pyrimidinone derivatives. Readily accessible reactants and simple reaction conditions make this synthetic procedure attractive.

EXPERIMENTAL SECTION

Mps were determined in capillaries using a Polman digital melting point apparatus (Model-mp-96). ^1H and ^{13}C NMR spectra were in $CDCl_3$ recorded on a Varian Gemini (300 and 100 MHz respectively) NMR spectrometer at ambient temperature using TMS as internal standard. Mass spectrometry (70 eV) was carried out on Perkin-Elmer Hitachi RMU-6L instrument. IR spectra were obtained in KBr pellets on Shimadzu 435 instrument. UV spectra were taken on Shimadzu 1601-PC model UV visible spectrometer. Elemental analysis was carried out in Indian Institute of Chemical Technology (IICT), Hyderabad, India. Reagents and solvents were of analytical grade. Solvents were dried before use.

Methyl 4-Amino-1-methyl-3-*n*-propyl pyrazole-5-carboxylate (1).- A mixture of 1-methyl-4-nitro-3-*n*-propyl pyrazole-5-carboxylic acid (11.3 g, 0.053 mol) and thionyl chloride (50 mL) was heated under reflux for 3 h. The reaction mixture was then cooled and excess thionyl chloride was removed *in vacuo*. The oily residue was cautiously added to methanol (75 mL) at 20-25°C and the resulting solution was concentrated to 1/3 of its volume. It was disolved in dichloromethane (100 mL) and was washed with 5% aqueous sodium carbonate solution (2 x 50 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to give methyl 1-methyl-4-nitro-3-*n*-propyl pyrazole-5-carboxylate[9] as a colorless solid. Recrystallization from *n*-hexane gave 10.3 g (86%) of colorless crystals, mp. 67-68°C.

^1H NMR ($CDCl_3$): d 0.96 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.8 (t, 2H, CH_2), 3.98 (s, 3H, OCH_3), 3.99 (s, 3H, N-CH_3); IR (KBr, cm^{-1}): 1731 (C=O).

To a solution of methyl 1-methyl-4-nitro-3-*n*-propyl pyrazole-5-carboxylate (10 g, 0.044 mol) in methanol (100 mL), was added Raney nickel (2 g) and the reaction mixture was placed under a hydrogen (25 psi) atmosphere in a Paar hydrogenation apparatus for 2.5 h. The reaction mixture was filtered through a Celite bed and the catalyst was washed with methanol (25 mL). The combined filtrates were concentrated to one-fourth of the original volume, the resulting residue was dissolved in water (25 mL) and extracted with dichloromethane (2 x 25 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated *in vacuo* to furnish 7.1 g (82%) of ester **1** as a brown colored oil. A small amount of crude ester **1** was purified by silica gel column chromatography using hexanes/EA (7:3) as eluent and was used for characterization.

^1H NMR ($CDCl_3$): δ 0.96 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.5 (t, 2H, CH_2), 2.9 (s, 2H, NH_2), 3.9 (s, 3H, OCH_3), 4.0 (s, 3H, N-CH_3); IR (KBr, cm^{-1}): 3459, 3330 (NH_2), 1684 (C=O).

Anal. Calcd. for $C_9H_{15}N_3O_2$: C, 54.80; H, 7.66; N, 21.30. Found: C, 55.06; H, 7.69; N, 21.42

6-Aryl-1-methyl-3-*n*-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-ones (2).

General Procedure.- A mixture of methyl 4-amino-1-methyl-3-*n*-propyl pyrazole-5-carboxylate (**1**, 1.97 g, 0.01 mol), aromatic primary amine (0.01 mol) and triethyl orthoformate (0.12 mol) in

xylene (25 mL) was heated under reflux for 6 h. The reaction mixture was cooled and diluted with *n*-hexane (25 mL). The separated pyrazolopyrimidine derivative **2** was collected and recrystallized from a suitable solvent (*Table 1*).

Table 1. Yields, mps and Elemental Analyses of Compounds **2a-2h**

Cmpd	Yield (%)	mp (°C)	Elemental Analysis (Found) C	H	N
2a	78	164-165[a]	68.06 (68.29)	6.42 (6.36)	19.84 (19.99)
2b	76	93-94[b]	67.14 (67.31)	6.00 (6.05)	20.87 (20.72)
2c	74	100-101[b]	68.06 (68.31)	6.42 (6.33)	19.84 (19.89)
2d	68	80-82[b]	68.06 (68.29)	6.42 (6.30)	19.84 (19.99)
2e	87	149-150[a]	59.50 (59.78)	4.99 (4.91)	18.50 (18.42)
2f	79	150-151[a]	56.27 (56.53)	5.27 (5.32)	15.44 (15.31)
2g	89	197-198[b]	62.17 (62.38)	6.13 (6.22)	17.06 (17.11)
2h	82	149-150[a]	64.41 (64.54)	6.08 (6.15)	18.77 (18.64)

Recrystallization solvents: a = methanol; b = ethanol

Table 2. Spectral Data of Compounds **2a-h**

Cmpd	IR (cm^{-1})	UV λ_{max}	^1H NMR δ ppm	^{13}C NMR δ ppm	MS
2a	1700	269	1.0 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.4 (s, 3H, Ar-CH_3), 2.9 (t, 2H, CH_2), 4.2 (s, 3H, N-CH_3), 7.4 (m, 4H, Ar-H), 7.8 (s, 1H, methine proton)	13.7, 20.9, 22.2, 27.4, 38.1, 125.3, 126.8, 129.9, 134.2, 136.9, 143.7, 146.0, 153.3	282 (M+), 267, 254, 118, 91, 79, 69, 65, 53
2b	1701	270	1.0 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.9 (t, 2H, CH_2), 4.3 (s, 3H, N-CH_3), 7.4 (d, 2H, Ar-H), 7.5-7.6 (m, 3H, Ar-H), 7.8 (s, 1H, methine proton)	13.9, 22.4, 27.5, 38.3, 125.4, 127.2, 129.1, 129.5, 136.8, 137.0, 143.7, 146.2, 153.6	
2c	1697	269	1.0 (t, 3H, CH_3), 1.8 (m, 2H, -CH_2), 2.4 (s, 3H, Ar-CH_3), 2.9 (t, 2H, CH_2), 4.2 (s, 3H, N-CH_3), 7.1 (d, 1H, Ar-H), 7.2 (s, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.4 (t, 1H, Ar-H), 7.8 (s, 1H, methine proton)	13.8, 21.1, 22.3, 27.5, 38.2, 124.1, 125.3, 127.7, 129.2, 129.8, 136.7, 136.9, 139.6, 143.7, 146.1, 153.6	282 (M^+), 267, 254, 253, 239, 118, 116, 91, 77, 65, 57
2d	1700	271	1.0 (s, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.2 (s, 3H, Ar-CH_3), 2.9 (t, 2H, CH_2), 4.25 (s, 3H, N-CH_3), 7.2-7.4 (m, 4H, Ar-H), 7.6 (s, 1H, methine proton)	13.7, 20.8, 22.4, 27.4, 38.2, 125.1, 125.7, 127.3, 129.8, 134.7, 135.4, 136.5, 138.9, 143.5, 146.1, 153.3	
2e	1695	272	0.85 (t, 3H, CH_3), 1.6 (m, 2H, CH_2), 2.7 (t, 2H, CH_2), 4.0 (s, 3H, N-CH_3), 7.2 (d, 2H, J = 11.5 Hz, Ar-H), 7.9 (d, 2H, J = 11.5 Hz, Ar-H), 8.2 (s, 1H, methine proton)	13.7, 22.2, 27.4, 38.2, 125.0, 128.4, 129.6, 134.9, 135.2, 136.8, 143.1, 146.1, 153.2	302 (M^+), 287, 274, 259, 111, 98, 85, 81, 73, 69, 60, 55, 43

Table 2. Continued...

Cmpd	IR (cm^{-1})	UV λ_{max}	^1H NMR δ ppm	^{13}C NMR δ ppm	MS
2f	1697	276	1.0 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.8 (t, 2H, CH_2), 3.7 (s, 3H, Ar-OCH_3), 3.8 (s, 3H, Ar-OCH_3), 4.2 (s, 3H, N-CH_3), 6.4 (s, 1H, Ar-H), 6.6 (s, 1H, Ar-H), 7.4 (s, 1H, methine proton)	13.9, 22.4, 27.5, 38.3, 55.7, 56.1, 98.3, 105.1, 116.5, 125.7, 129.4, 134.4, 136.7, 137.0, 144.8, 146.1, 153.1	
2g	1703	274	1.0 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.7 (t, 2H, CH_2), 3.9 (s, 3H, Ar-OCH_3), 3.95 (s, 3H, Ar-OCH_3), 4.2 (s, 3H, N-CH_3), 6.9 (d, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.4 (s, 1H, Ar-H), 8.3 (s, 1H, methine proton)	13.7, 21.8, 27.4, 38.2, 55.7, 56.2, 104.4, 109.9, 112.1, 125.5, 127.5, 136.2, 139.3, 143.4, 145.5, 153.4	328 (M^+), 313, 300, 285, 164, 149, 136, 94, 77, 65, 53
2h	1697	288	0.9 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.9 (s, 3H, Ar-OCH_3), 4.2 (s, 3H, N-CH_3), 6.9 (d, 2H, J = 11.5 Hz, Ar-H), 7.3 (d, 2H, J = 11.5 Hz, Ar-H), 8.3 (s, 1H, methine proton)	13.7, 22.3, 27.4, 38.2, 55.7, 108.6, 125.0, 125.3, 129.1, 134.3, 136.5, 143.5, 146.2, 153.2	

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