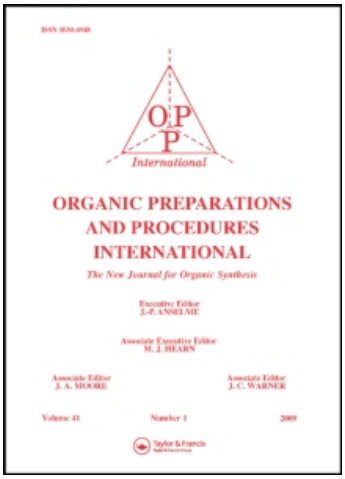

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A FACILE METHOD WITH IMPROVED YIELDS IN THE SYNTHESIS OF 6-ARYLPYRIDO[2',3':4,5]PYRIMIDO[1,6-a]BENZIMIDAZOLES

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A FACILE METHOD WITH IMPROVED YIELDS IN THE SYNTHESIS OF 6-ARYLPYRIDO[2',3':4,5]PYRIMIDO[1,6-a]BENZIMIDAZOLES†

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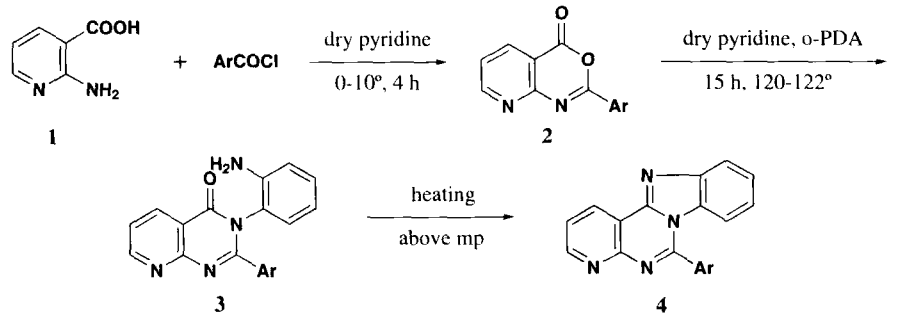
Methylxanthines are a major class of bronchodilators employed in the treatment of asthma despite a narrow therapeutic index. New heterocyclic compounds designed on the basis of the xanthine skeleton are being investigated as possible bronchodilators with a wider margin of safety.[1] In continuation of our work on the synthesis and bronchodilator activity of some new fused quinazolines,[2] we carried out the preparation of some fused pyridopyrimidines as isosteres of the quinazoline moiety. A literature survey revealed that the title compounds (**4**) have been synthesized with overall yields of about 34%.[3,4] We now report the preparation of the above compounds by a route analogous to the synthesis of benzimidazoquinazolines,[2] involving mild reaction conditions and easy work-up procedures with improved overall yields (46-70%).



1 2 3 4

a) Ar = -C_6H_5 b) Ar = *p*-NO_2-C_6H_4 c) Ar = *p*-Cl-C_6H_4 d) Ar = *p*-Me-C_6H_4

EXPERIMENTAL SECTION

Melting points were determined in open capillaries on a Thermonik Precision Melting Point cum Boiling Point Apparatus-Model C-PMB-2 and are uncorrected. Column chromatography and tlc were performed on silica gel (230-400 mesh) and on precoated plates (E. Merck Kieselgel 60 F_{254}) respectively. IR spectra were recorded using KBr pellets on Perkin-Elmer Infrared 337 spectrophotometer and ^{1}H NMR spectra were recorded on a Varian EM 390 90 MHz spectrometer using TMS as internal standard and the chemical shift values expressed in δ ppm. Mass spectra (EIMS) were recorded on Jeol D-300 spectrometer at 70 eV. Elemental analyses was carried out using Heraus Carlo Erba 1108 CHN analyser. The starting material, 2-aminonicotinic acid was procured from Janssen Chimica, Belgium.

2-Arylpyrido[2,3-b]1,3-oxazin-8-one (2).- The respective arylcarboxylic acid chloride (10 mmol) was added dropwise to a solution of 2-aminonicotinic acid (1.38 g, 10 mmol) in dry pyridine (20 mL) with continuous stirring for 4 hrs under ice-cold conditions. The reaction mixture was poured onto ice-cold water (150 mL) and the crystalline product was collected and recrystallized from methanol.

6-Aryl-(2-aminophenyl)pyrido[2',3'-b]-7H-pyrimidin-8-ones (3).- Compound **2** (2.0 mmol) was reacted with *o*-phenylenediamine (0.324 g, 3.0 mmol) in dry pyridine by refluxing for 15 hrs. Excess solvent was removed under reduced pressure and the residue obtained was dissolved in crushed ice. The pH was adjusted to 7 by neutralization with glacial acetic acid and the solid product obtained was collected and recrystallized from methanol, except **3b** which was carried out in DMSO.

6-Arylpyrido[2',3':4,5]pyrimido[1,6-a]benzimidazole (4).- Compound **3** (1.0 mmol) was heated above its melting point under anhydrous conditions for 15 min. The solid residue obtained on cooling to room temperature was triturated with petroleum ether and recrystallized from methanol.

TABLE 1. Yields, mps. and Elemental Analyses of Compounds **2-4**

Cmpd	Yield	mp.[a]	Elemental Analyses (Found)		
	(%)	(°C)	C	H	N
2a	70	141	69.64 (69.51)	3.57 (3.62)	12.50 (12.61)
2b	90	231	57.99 (57.72)	2.60 (2.51)	15.61 (15.74)
2c	86	201	60.35 (60.51)	2.71 (2.62)	10.83 (l0.65)
2d	84	187	70.59 (70.68)	4.20 (4.35)	11.76 (11.82)
3a	74	203	72.61 (72.46)	4.46 (4.52)	17.83 (17.99)
3b	85	283[b]	63.51 (63.26)	3.62 (3.48)	19.50 (19.41)
3c	78	241	65.42 (65.26)	3.73 (3.89)	16.06 (16.21)
3d	73	234	73.17 (73.29)	4.88 (4.95)	17.07 (17.16)
4a	89	24l[c]	77.03 (77.26)	4.05 (4.19)	18.92 (18.78)
4b	92	>300[c]	66.86 (66.61)	3.22 (3.39)	20.53 (20.65)
4c	88	242[c]	68.99 (68.82)	3.33 (3.11)	16.94 (16.79)
4d	84	26l[c]	77.42 (77.39)	4.52 (4.61)	18.06 (18.25)

a) Recrystallized from methanol except where noted. b) Recrystallized from DMSO. c) Lit.[3] mp. 4a-259°, 4b-284°, 4c-278°, 4d-236°.

TABLE 2. Mass Spectral Data of Compounds **4**[a]

Cmpd	Mass Spectrum [m/e (ion %)]
4a	297 (M^++1, 20.9), 296 (M^+, 100), 295 (M^+-H, 78.1), 268 (295-HCN, 2.3), 193 (M^+-C_6H_5-CN, 13.7), 166 (193-HCN, 9.8), 103 ($PhCN^+$, 14), 77 (Ph, 12).
4b	342 (M^++1, 18.5), 341 (M^+, 95.4), 340 (M^+-H, 14.1), 311 (M^+-NO, 30.3), 310 (340-NO, 34.9), 296 (342-NO_2, 27.5), 295 (M^+-NO_2, 39.6), 294 (M^+-NO_2, 52.1), 283 (311-CO, 6.1), 282 (310-CO, 8.4), 194 (342-NO_2-C_6H_4-CN, 10), 193 (M^+-NO_2-C_6H_4-CN, 23.6), 166 (193-HCN, 13), 148 (NO_2-C_6H_4-CN, 6.2), 104 (Ph-CN, 18), 77 (Ph, 19).
4c	333 (M^++3, isotopic, 7), 332 (M^++2, isotopic, 32.8), 331 (M^++1, 42.6), 330 (M^+, 100), 329 (M^+-H, 73.6), 193 (M^+-Cl-C_6H_5-CN, 66), 166 (193-HCN, 19), 104 (Ph-CN, 18), 77 (Ph, 15).
4d	310 (M^+, 2.1), 209 (M^+-101, 28), 208 (M^+-102, 100), 193 (M^+-H_3C-C_6H_4CN, 3.7), 166 (193-HCN, 0.8), 117 (H_3C-C_6H_4-CN, 2.7), 104 ($PhCN^+$, 10.7), 91 (C_7H_7, 11), 77 (Ph, 4.3).

a) Spectral Data for **4b**: IR (KBr):3054 (Ar-H), 1625, 1594 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.5-8.0 (m, 8H, Aromatic), 6.9 (d, 1H, C_2-H), 9.0 (s, 2H, C_1 and C_3-H).

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