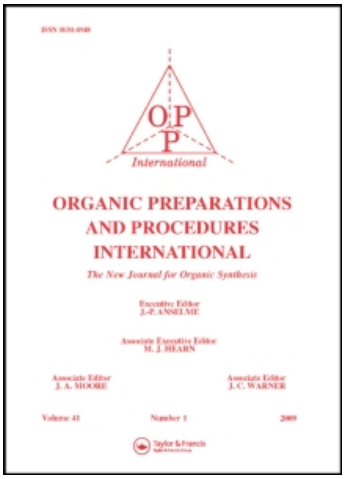

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AN EFFICIENT SYNTHESIS OF N'-(*o*-ALKOXYPHENYL)-PYRIDINECARBOXAMIDINE DERIVATIVES

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AN EFFICIENT SYNTHESIS OF N'-(o-ALKOXYPHENYL)-PYRIDINECARBOXAMIDINE DERIVATIVES

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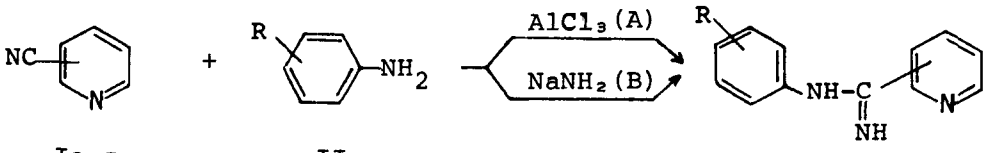
N'-Aryl-pyridinecarboxamidines (III) are of current interest because of their useful biological properties,[1] and because they can serve as precursors of the corresponding benzimidazoles.[2] While the aluminum chloride-catalyzed condensation of



Ia-c II IIIa-c to VIIa-c

R = CH_3, C_2H_5 a) 2-pyridyl; b) 3-pyridyl; c) 4-pyridyl

cyanopyridines (I) with anilines (II) proceeds well in some cases,[3-5] dealkylation of o-alkoxyanilines does occur in the presence of aluminum chloride.[6] We now report the condensation of I with II in the presence of sodium amide (method B).[1,7]

The IR spectra of the amidines display C=N and NH absorptions at 1648-1616 cm^{-1} and 3480-3415 and 3385-3240 cm^{-1}. In contrast to previous reports,[5,8] the C=N double bond absorption showed little sensitivity to changes in the substituent groups. The nmr spectra showed a broad single hydrogen peak at δ 7.00-6.00 for two protons of the amino group, which disappeared readily upon the addition of D_2O.

EXPERIMENTAL

All melting points were uncorrected. IR Spectra were recorded on Nippon Bunko DS-701G Infrared Spectrophotometer and ^{1}H-NMR spectra were taken with JNM-C-60H in ca 4% (w/v) DMSO-d_6 with tetramethylsilane as an internal standard. MS spectra were taken with JEOL-JMS-01SG Spectrometer.

N'-(Alkoxyphenyl)pyridinecarboxamidines. Method A.- In general, N'-(m- or p-alkoxyphenyl)pyridinecarboxamidines were prepared by the condensation of m- or p-alkoxyaniline (0.1 mole) with a cyanopyridine (0.1 mole) in the presence of anhydrous $AlCl_3$ (0.1 mole) in sym-tetrachloroethane (40 ml) under reflux for 30 min, according to the method previously described[5] (TABLE 1). Method B.- Powdered $Fe(NO_3)_3 \cdot 9H_2O$ (0.2 g) was added to 350 ml of liq. NH_3 with stirring and then 2.3 g (0.1 mole) of powdered sodium was added gradually for 10 min, during which period granular sodium amide separated. A suspension of 0.1 mole of an alkoxyaniline in 50 ml of Et_2O was added to the mixture by portions and stirred for 3 hrs. A suspension of 10.4 g (0.1 mole) of a cyanopyridine in 100 ml of Et_2O was then added by

TABLE 1. Physical Constants of N'-(Alkoxyphenyl)pyridine-carboxamidines.

Compd.	R	mp.(°C)	Appearance[f]	Yield(%) Method A	Yield(%) Method B	Analysis(%) Calcd.(Found) C	H	N
IIIa	o-OCH_3	94	needles[a]	-	81	68.70	5.77	18.49
						(68.93)	(5.84)	(18.73)
IIIb	o-OCH_3	104-105	prisms[a]	-	61	(68.67)	(5.73)	(18.27)
IIIc	o-OCH_3	124.5	plates[a]	-	65	(68.89)	(5.81)	(18.26)
IVa	m-OCH_3	65-66	prisms[b]	63	63	(68.48)	(5.51)	(18.37)
IVb	m-OCH_3	128-129	prisms[a]	54	72	(68.88)	(5.77)	(18.29)
IVc	m-OCH_3	149	prisms[c]	53	74	(68.90)	(5.79)	(18.25)
Va	p-OCH_3	78.5-80	needles[b]	75	70	(68.53)	(5.56)	(18.19)
Vb	p-OCH_3	143-144	plates[a]	32	79	(68.61)	(5.49)	(18.20)
Vc	p-OCH_3	148-149	prisms[d]	36	81	(68.73)	(5.51)	(18.20)
VIa	o-OC_2H_5	63-64	needles[e]	-	69	69.69	6.27	17.41
						(69.83)	(6.37)	(17.44)
VIb	o-OC_2H_5	65-66	prisms	-	70	(69.85)	(6.42)	(17.58)
VIc	o-OC_2H_5	106-107	needles[a]	-	78	(69.90)	(6.30)	(17.41)
VIIa	p-OC_2H_5	94-95	needles[a]	73	67	(69.89)	(6.16)	(17.17)
VIIb	p-OC_2H_5	128-130	plates[a]	57	61	(69.58)	(6.32)	(17.30)
VIIc	p-OC_2H_5	146-148	prisms[c]	63	84	(69.49)	(6.35)	(17.66)

a) From acetone-n-hexane b) From ether-n-hexane c) From acetone d) From benzene-methanol e) From ether f) colorless

portions and further stirred for 3 hrs. After the reaction was over, 5.4 g of NH_4Cl was added to quench and the liq. NH_3 was allowed to evaporate. The residue was treated with 100 ml of Et_2O, then shaken with 100 ml of H_2O. The separated product was collected and recrystallized to give an analytical sample (TABLE I).

Dealkylation of o-Anisidine by Aluminum Chloride.- Powdered anhydrous $AlCl_3$ (6.7 g, 0.05 mole) was added to a solution of

6.2 g (0.05 mole) of o-anisidine in 22 ml of sym-tetrachloroethane and the mixture was refluxed for 30 min. The reaction mixture was poured into 500 ml of 5N NaOH aq. solution and extracted with CH_2Cl_2 to remove unchanged o-anisidine. The alkaline aqueous layer was neutralized by HCl to pH 7 and extracted with CH_2Cl_2. The extract was dried over anhydrous K_2CO_3 and evaporated in vacuo. The residue upon trituration with a small amount of a mixture of Et_2O and pet. ether. solidified. The resulting solid was collected and recrystallized from Et_2O-pet. ether to give an analytical sample, mp. 173-174°, which gave no depression of the mp. with o-aminophenol (mp. 174°). The IR, nmr and MS spectra were also identical with those of o-aminophenol in all respects.

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A SYNTHESIS OF FUSED PYRIMIDINES

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Many of the reported synthetic methods for the preparation of pyrazolo(3,4-d)pyrimidines start with a 5-aminopyrazole with an electron-withdrawing reactive substituent at position 4 (I). Condensation of these 5-aminopyrazoles with appropriate reactants such as ureas or suitable analogues leads to the desired heterocycle (II).[1] An important member of this class of compounds, pyrazole(3,4-d)pyrimidin-4(5H)-one (or its hydroxy tautomer, allopurinol, an isostere of 6-hydroxypurine or hypoxanthine) is a good inhibitor of xanthine oxidase[2] and has been in clinical use under the brand name, "Zyloprim", a drug for the relief of gout.[3] Several derivatives of it have been prepared and shown to exhibit xanthine oxadase inhibitory properties.[4]