Journal of Fluorine Chemistry, *41* (1988) 303–310

Received: January 7, 1988; accepted: July 6, 1988

A NOVEL SYNTHESIS OF FLUORINATED PYRIDO [2,3-d] PYRIMIDINE DERIVATIVES

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SUMMARY

Fluorinated 4-imino-3,5,7-trisubstituted-pyrido [2,3-d] pyrimidine-2(1H)thiones have been synthesised in good yields by the reaction of 2-amino-3-cyano-4,6-disubstituted-pyridines with various arylisothiocyanates. These new type of products have been characterised by elemental analysis, IR, ^{1}H and ^{19}F NMR spectral studies.

INTRODUCTION

A survey of the literature reveals that pyrido[2,3-d] pyrimidines possess diverse biological activities such as bactericidal [1], fungicidal [2], antiallergic [3], antihypertensive [4] etc. In the recent years, antimalarial [5] and antileukemic [6] activities have also been reported. Fluorinated organic compounds which have a great utility in the field of therapy are well known, and this prompted us to synthesise some new fluorinated pyrido [2,3-d] pyrimidines, in the hope of finding better therapeutic values. The general method of preparation is described in Scheme-1.

2-Amino-3-cyano-4,6-disubstituted pyridines (I) have been synthesised from α,β-unsaturated ketones and malononitrile in the presence of an excess of ammonium acetate through Michael reactions [7]. Arylisothiocyanates were prepared by usual methods [8].

2-Amino-3-cyano-4,6-disubstituted pyridines (I) on refluxing with appropriate arylisothiocyanates in 1:1 molar

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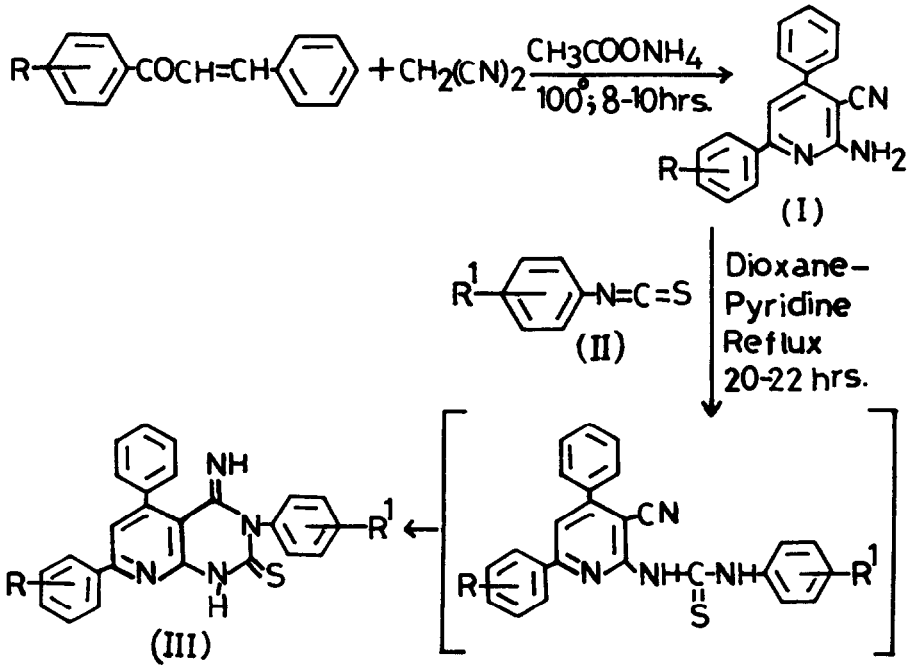

Scheme 1

ratio in the presence of 1,4-dioxane and pyridine have afforded the title compounds, without separating the intermediate pyridylthioureas (see Table 1).

EXPERIMENTAL

Synthesis of 2-Amino-3-cyano-4,6-disubstituted-pyridines [7]

A mixture of an α,β-unsaturated ketone (0.1 mol), malononitrile (0.1 mol), ammonium acetate (0.8 mol) and ethanol (100 ml) was heated on a water bath for about 8-10 hours. The contents of the flask were poured into crushed ice with constant stirring to obtain the solid yellow mass, washed repeatedly with water and the residue was recrystallised from dimethylformamide-ethanol (1:2) giving yellow crystals. The following cyanopyridines have been synthesised.

(Ia) 2-Amino-3-cyano-4-phenyl-6-(p-fluorophenyl) pyridine, m.p. 210°C; yield 35%.

(Ib) 2-Amino-3-cyano-4,6-diphenylpyridine, m.p. 176°C; yield 33%.

(Ic) 2-Amino-3-cyano-4-phenyl-6-(p-methylphenyl)pyridine, m.p. 160°C; yield 34%.

(Id) 2-Amino-3-cyano-4-phenyl-6-(p-methoxyphenyl) pyridine, m.p. 170°C; yield 36%.

(Ie) 2-Amino-3-cyano-4-phenyl-6-(p-bromophenyl) pyridine, m.p. 187°C; yield 28%.

These 5 compounds Ia-Ie when characterised by elemental analysis, IR and ^{1}H NMR spectral studies, gave results similar to those reported in the literature [7].

Synthesis of Arylisothiocyanates [8]

Method 1

A mixture of carbon disulphide (0.36 mol) and 45 ml of concentrated ammonia solution (d 0.88) was cooled in an ice-salt bath. To this, the arylamine (0.3 mol) was added dropwise with stirring mechanically during about 20 minutes. The mixture was stirred for further 30 minutes and allowed to stand for another 30 minutes. A heavy precipitate of ammonium aryldithiocarbamate was separated out. It was transferred to a 2-litre r.b. flask by four extractions with 100 ml portions of water. To this, the solution of lead nitrate (0.31 mol) in 200 ml of water was added with stirring. The reaction mixture was stirred for an additional hour. The mixture was steam distilled into a receiver containing 5 ml of ca. 0.5 M-sulphuric acid as long as organic material passed over (2 litres of distillate). The oil was separated and dried over anhydrous calcium chloride and distilled under diminished pressure. The following arylisothiocyanates were prepared by this method.

(IIa) Phenyl isothiocyanate , b.p. 221°C; yield 76%.

(IId) o-Tolyl isothiocyanate, b.p. 239°C; yield 65%.

(IIe) m-Tolyl isothiocyanate, b.p. 241°C; yield 58%.

(IIg) p-Fluorophenyl isothiocyanate, m.p. 26-28°C, b.p. 228°C; yield 50%.

Method 2

The following arylisothiocyanates were prepared by the method described for the preparation of p-bromophenyl isothiocyanate in Vogel's Practical Organic Chemistry [8]:

(IIb) p-Chlorophenyl isothiocyanate, m.p. 47°C; yield 70%.

(IIc) p-Bromophenyl isothiocyanate, m.p. 60°C; yield 73%.

[a](IIf) p-Tolyl isothiocyanate, m.p. 25-26°C, b.p.237°C, yield 60%.

The IR and ^{1}H NMR spectral data of the arylisothiocyanates (IIa-IIg) are consistent with their structures.

Synthesis of 4-Imino-3,5,7-trisubstituted-pyrido[2,3-d] pyrimidine-2(1H)-thiones

A mixture of the 2-amino-3-cyano-4,6-disubstituted-pyridine (I;0.01 mol), the appropriate arylisothiocyanate (II;0.01 mol), dioxane (15.0 ml) and pyridine (2.0 ml) was refluxed for 20-22 hours. After cooling, it was poured into crushed ice, the precipitated solid was filtered off and washed repeatedly with water. The dried crude product was recrystallised from dimethylformamide-ethanol (2:1).

All the synthesised compounds (III) are new. They are yellow or brown coloured, high melting solids giving one spot on TLC. The characterisation and analytical data are given in Table 1.

SPECTROSCOPIC ANALYSIS

The IR spectra were recorded by using KBr pellets. All of the pyrido [2,3-d] pyrimidines synthesised exhibit a band in the region 3380-3320 cm^{-1} corresponded to >NH stretching and a broad band in the region 3120-3100 cm^{-1} corresponded to >C=NH stretching vibrations. The C=S group frequency was observed at 1195-1180 cm^{-1} and three bands were observed in the region 1580-1405 cm^{-1} due to the -NH-C=S group. The absorp-

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[a]After steam distillation p-tolyl isothiocyanate was collected by the procedure as described in method 1.

TABLE 1

Characterisation and analytical data of compounds (III) (New compounds)

Reactants		Product No.	R	R^1	Molecular Formula	m.p.[a] °C	Yield %	Analysis % Calcd.(Found) C	H	N
Ia	IIa	IIIa	4-F	H	$C_{25}H_{17}FN_4S$	295	68	70.74 (71.06)	4.04 (4. 32)	13.20 (13.70)
Ia	IIb	IIIb	4-F	4-Cl	$C_{25}H_{16}ClFN_4S$	315	65	65.43 (65.73)	3.51 (3.81)	12.21 (12.66)
Ia	IIc	IIIc	4-F	4-Br	$C_{25}H_{16}BrFN_4S$	300	69	59.65 (59.99)	3.20 (2.95)	11.13 (10.70)
Ia	IId	IIId	4-F	2-CH_3	$C_{26}H_{19}FN_4S$	213	67	71.21 (70.88)	4.37 (4.60)	12.78 (12.31)
Ia	IIe	IIIe	4-F	3-CH_3	$C_{26}H_{19}FN_4S$	272	65	71.21 (71.49)	4.37 (4.10)	12.78 (12.29)
Ia	IIf	IIIf	4-F	4-CH_3	$C_{26}H_{19}FN_4S$	213	68	71.21 (71.55)	4.37 (4.67)	12.78 (12.28)
Ib	IIg	IIIg	H	4-F	$C_{25}H_{17}FN_4S$	275	69	70.74 (70.42)	4.04 (3.78)	13.20 (13.62)
Ic	IIg	IIIh	4-CH_3	4-F	$C_{26}H_{19}FN_4S$	312	68	71.21 (70.92)	4.37 (4.61)	12.78 (13.22)
Id	IIg	IIIi	4-OCH_3	4-F	$C_{26}H_{19}FN_4OS$	302	69	68.71 (69.05)	4.21 (4.49)	12.33 (11.83)
Ie	IIg	IIIj	4-Br	4-F	$C_{25}H_{16}BrFN_4S$	290	65	59.65 (59.97)	3.20 (2.90)	11.13 (11.58)

[a] Melting points are uncorrected.

TABLE 2

The IR, ^{1}H and ^{19}F spectral data of compounds (III)

Comp. No.	IR (KBr : ν max cm^{-1})					^{1}H NMR (ppm from TMS)[a]				^{19}F NMR(ppm)
	>NH	>C=NH	C=S	-NH-C=S	C-F	>NH	>C=NH	-ArH	$-CH_3$ $-OCH_3$	Ar-F
IIIa	3360	3100	1195	1405,1435,1560	1230	8.74-9.03(d)		7.63-8.38(m)	-	-106.339
IIIb	3330	3100	1190	1440,1490,1555	1225	8.80-9.15(d)		7.34-8.50(m)	-	-106.744
IIIc	3320	3100	1190	1430,1490,1550	1220	8.83(s)8.94(s)		7.63-8.65(m)	-	-106.765
IIId	3330	3120	1185	1440,1485,1555	1220	7.97-8.27(d)		6.97-7.94(m)	2.07(s)	-107.787
IIIe	3340	3110	1190	1430,1490,1555	1220	8.79-9.01(d)		7.31-8.45(m)	2.68(s)	-106.512
IIIf	3320	3100	1180	1440,1500,1580	1225	7.97(s)8.04(s)		6.80-7.81(m)	2.21(s)	-107.654
IIIg	3370	3110	1195	1440,1490,1560	1250	8.60-8.88(d)		7.36-8.34(m)	-	-113.636
IIIh	3340	3120	1185	1450,1490,1560	1250	8.47-8.76(d)		7.40-8.25(m)	2.77(s)	-113.984
IIIi	3380	3120	1185	1450,1500,1550	1250	8.03(s)8.13(s)		6.66-7.82(m)	3.84(s)	-113.579
IIIj	3320	3100	1180	1420,1470,1550	1240	8.56(s)8.67(s)		7.50-8.63(m)	-	-113.636

[a] The ^{1}H NMR spectra of the compounds IIa-IIc, IIe and IIg-IIh were recorded in DMSO-d_6 and the rest in $CDCl_3$+TFA.

s = singlet, d = doublet, m = multiplet

tion due to the C-F linkage was observed in the region 1250-1220 cm^{-1}.

The ^1H NMR spectra were recorded in DMSO-d_6 and in $CDCl_3$+TFA using TMS as an internal standard. The chemical shifts are given in ppm downfield from tetramethylsilane. The resonances of the >NH and >C=NH protons occurred in the range of δ 7.97-9.15 ppm. Aromatic protons occurred as a multiplet in the range of δ 6.66-8.65 ppm, whereas the CH_3 protons occurred as a singlet in the range of δ 2.07-2.77 ppm and OCH_3 protons as a singlet at δ 3.84 ppm.

In the ^{19}F NMR spectra of the compounds IIIa-IIIf, a characteristic signal was observed in the range of δ -106.339 to δ -107.787 ppm, and in the compounds IIIg-IIIj, a signal was observed in the range of δ -113.579 to δ -113.984 ppm assigned to the fluorine atom carried on the phenyl ring. The ^{19}F NMR spectra were recorded in DMSO and the values are relative to hexafluorobenzene used as an external standard. The spectroscopic data are given in Table 2. All these data confirmed the structure III for the prepared compounds.

IR spectra were recorded on a Perkin-Elmer 557 grating infrared spectrophotometer, ^1H and ^{19}F NMR spectra were scanned on FX 90 Q JEOL type spectrometer (at 90 MHz).

ACKNOWLEDGEMENT

Financial support from University Grants Commission, New Delhi is gratefully acknowledged.

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