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Received January 26, 1987

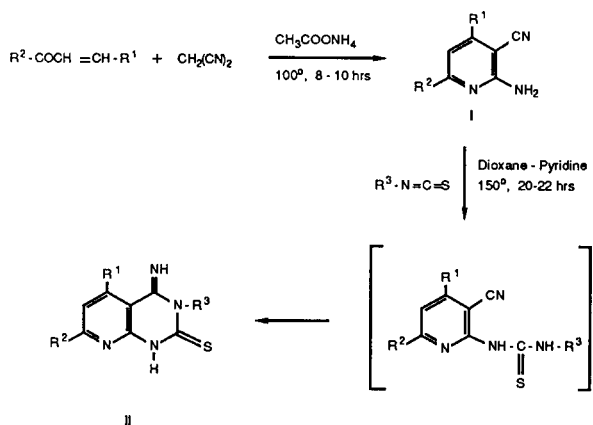
The synthesis of 4-imino-3,5,7-trisubstituted-pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones is described. The elemental analysis, ir and nmr spectral data confirm the structure of the products.

J. Heterocyclic Chem., **24**, 1169 (1987).

Only a few pyrido[2,3-*d*]pyrimidines have been synthesized [1-7] and these are found to be active against a variety of pathogenic bacteria. Pyrido[2,3-*d*]pyrimidines having fungicidal [8], bactericidal [9], antiinflammatory and analgesic [10], and immuno suppressing activities [11] have also been prepared. During the last few years a growing number of useful applications of pyridopyrimidines [12-14] has increased the desirability of the preparation of a new type of pyrido[2,3-*d*]pyrimidines, and therefore the iminopyrido[2,3-*d*]pyrimidines were selected for the present investigation.

In the present work, various 4-imino-3,5,7-trisubstituted-pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones have been synthesized, without separating intermediate pyridylthioureas, according to the following general Scheme 1.

Scheme 1



α,β -Unsaturated ketones and dicyanomethane reacted in a 1:1 molar ratio to give 2-amino-3-cyano-4,6-disubstituted-pyridines **I** through a Michael reaction with the elimination of 1 mole each of water and hydrogen [15]. Compound **I** reacted with the appropriate isothiocyanate to give 4-imino-3,5,7-trisubstituted-pyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones **II**.

The structure of all these compounds were confirmed by their analytical and spectral data. The ir spectra of the compounds show some characteristic peaks, indicating the presence of a particular functional group. All of the

pyrido[2,3-*d*]pyrimidines synthesized exhibit bands in the region 1420-1570 cm^{-1} , which are due to -NHC=S group while the C=S linkage gave absorption in the region 1180-1200 cm^{-1} . No band was observed in the region 2600-2550 cm^{-1} , corresponding to the C-SH moiety in any of the spectra and therefore, it is concluded the thione (C=S) structure is present in the pyrido[2,3-*d*]pyrimidine-2(*H*)-thiones synthesized. The nmr spectra in DMSO- d_6 show that the resonances of the CH_3 protons occur as a singlet at δ 3.5 ppm, the OCH_3 protons occur as a singlet at δ 4.29 ppm, the phenyl protons occur as a multiplet in the region δ 7.37-8.38 ppm, the >N-H proton occurs as a singlet at δ 8.74 ppm and imino group (>C=NH) proton occur as a singlet at δ 8.84 ppm.

EXPERIMENTAL

Melting points were determined in sealed evacuated capillary tubes and are uncorrected. Infrared spectra were determined by means of pressed potassium bromide disks on a Perkin-Elmer Model 137 B Infracord Spectrophotometer. The nmr spectra have been recorded on FX 90Q Jeol type spectrometer, using tetramethylsilane as an internal standard. The chemical shifts are given in ppm downfield from tetramethylsilane.

Synthesis of 2-Amino-3-cyano-4,6-disubstituted-pyridines. **I**.

2-Amino-3-cyano-4-phenyl-6-(*p*-methylphenyl)pyridine (**Ia**).

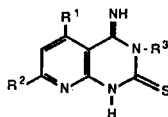
A mixture of dicyanomethane 6.6 g (0.1 mole), 4'-methylchalcone 22.2 g (0.1 mole) and ammonium acetate 61.6 g (0.8 mole) in 100 ml of ethanol was refluxed on a water bath for about 8 hours. The contents of the flask were poured into ice with constant stirring to obtain the solid yellow mass, washed with water and ethanol and the residue was crystallized from dimethylformamide-ethanol giving 9.69 g (34%) of yellow crystals, mp 160°; ir (potassium bromide): ν 3445, 3315, 3170 (NH_2), 2220 (C=N conjugated), 1600, 1590, 1585, 1475, 1440 (C=C conjugated); nmr (deuteriochloroform): δ 2.48 (s, CH_3 , 3H), 7.3 (s, =C-H, 1H), 7.5-7.7 (broad, NH_2 , 2H), 7.25 (s, C_6H_4 , 4H), 7.8-8.2 (d, C_6H_5 , 5H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{N}_3$: C, 80.0; H, 5.26; N, 14.74. Found: C, 80.2; H, 5.27; N, 14.92.

2-Amino-3-cyano-4-phenyl-6-(*p*-methoxyphenyl)pyridine (**Ib**).

A mixture of dicyanomethane 6.6 g (0.1 mole), 4'-methoxychalcone 23.8 g (0.1 mole) and ammonium acetate 61.6 g (0.8 mole) in 100 ml of ethanol was refluxed on a water bath for about 10 hours and worked up according to the procedure for **Ia** to give 10.84 g (36%), mp 170°; ir (potassium bromide): ν 3450, 3340, 3140 (NH_2), 2220 (C=N conjugated), 1600, 1565, 1530, 1500, 1440 (C=C conjugated); nmr (deuteriochloro-

Table 1
Characterization Data of Compounds II



Compound No.	R ¹	R ²	R ³	Yield (%)	MP [a] (°C)	Molecular formula	Analysis (%)		
							Calcd.	(Found)	
							C	H	N
IIa	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅	70	276	C ₂₆ H ₂₀ N ₄ S	74.29 (74.36)	4.76 (4.90)	13.33 (13.44)
IIb	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -ClC ₆ H ₄	68	318	C ₂₆ H ₁₉ ClN ₄ S	68.65 (68.70)	4.18 (4.25)	12.32 (12.50)
IIc	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -BrC ₆ H ₄	70	300	C ₂₆ H ₁₉ BrN ₄ S	62.53 (62.42)	3.18 (3.12)	11.22 (11.21)
IId	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	<i>o</i> -CH ₃ C ₆ H ₄	66	286	C ₂₇ H ₂₂ N ₄ S	74.65 (74.70)	5.07 (5.20)	12.90 (12.82)
IIe	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	<i>m</i> -CH ₃ C ₆ H ₄	65	283	C ₂₇ H ₂₂ N ₄ S	74.65 (74.62)	5.07 (5.12)	12.90 (12.83)
IIf	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	69	285	C ₂₇ H ₂₂ N ₄ S	74.65 (74.65)	5.07 (5.14)	12.90 (12.81)
IIg	C ₆ H ₅	<i>p</i> -OCH ₃ C ₆ H ₄	C ₆ H ₅	62	293	C ₂₆ H ₂₀ N ₄ OS	71.56 (71.30)	4.59 (4.70)	12.84 (12.72)
IIh	C ₆ H ₅	<i>p</i> -OCH ₃ C ₆ H ₄	<i>p</i> -ClC ₆ H ₄	71	287	C ₂₆ H ₁₉ ClN ₄ OS	66.31 (66.34)	4.04 (4.12)	11.90 (11.92)
IIi	C ₆ H ₅	<i>p</i> -OCH ₃ C ₆ H ₄	<i>p</i> -BrC ₆ H ₄	70	297	C ₂₆ H ₁₉ BrN ₄ OS	60.58 (60.47)	3.69 (3.62)	10.87 (10.80)
IIj	C ₆ H ₅	<i>p</i> -OCH ₃ C ₆ H ₄	<i>o</i> -CH ₃ C ₆ H ₄	67	278	C ₂₇ H ₂₂ N ₄ OS	72.00 (72.20)	4.89 (4.84)	12.44 (12.45)
IIk	C ₆ H ₅	<i>p</i> -OCH ₃ C ₆ H ₄	<i>m</i> -CH ₃ C ₆ H ₄	64	274	C ₂₇ H ₂₂ N ₄ OS	72.00 (72.30)	4.89 (4.80)	12.44 (12.40)
III	C ₆ H ₅	<i>p</i> -OCH ₃ C ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	69	290	C ₂₇ H ₂₂ N ₄ OS	72.00 (72.20)	4.89 (4.63)	12.44 (12.45)

[a] Melting points are uncorrected.

form): δ 3.85 (s, OCH₃, 3H), 7.18 (s, =CH; 1H), 7.5-7.7 (broad, NH₂, 2H), 6.9-7.1 (d, C₆H₄, 4H), 7.9-8.1 (d, C₆H₅, 5H).

Anal. Calcd. for C₁₉H₁₅N₃O: C, 75.75; H, 4.98; N, 13.95. Found: C, 75.55; H, 4.70; N, 13.62.

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

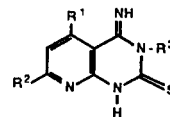
A mixture of 2-amino-3-cyano-4,6-disubstituted-pyridine (I) (0.01 mole), appropriate isothiocyanate (0.01 mole), dioxane (15.0 ml) and pyridine (2.0 ml) was refluxed in an oil bath at 150° for about 20-22 hours. The reaction mixture was cooled and poured into the crushed ice. The precipitated solid was filtered, washed repeatedly with water followed by sodium bicarbonate (5% w/v) and finally with water. The dried crude product was crystallized from glacial acetic acid. The characterization data and ir spectral data are given in Table 1 and Table 2 respectively.

Acknowledgement.

One of the authors (S.S.V.) is grateful to the University Grants Commission, New Delhi for awarding a Junior Research Fellowship.

Table 2

IR Spectra of Compounds II (Potassium bromide ν max^{cm⁻¹})



Compound No.	-NH	>C=NH	>C=S	-NH-C=S		
IIa	3360	3140	1200	1450,	1495,	1570
IIb	3340	3110	1180	1430,	1470,	1550
IIc	3350	3130	1200	1440,	1480,	1560
IId	3320	3110	1200	1430,	1480,	1560
IIe	3320	3100	1190	1420,	1470,	1555
IIf	3325	3100	1200	1430,	1470,	1560
IIg	3380	3120	1200	1440,	1485,	1560
IIh	3340	3120	1180	1430,	1470,	1570
IIi	3380	3130	1200	1480,	1510,	1560
IIj	3320	3100	1200	1430,	1470,	1555
IIk	3310	3110	1190	1420,	1475,	1560
III	3300	3120	1200	1420,	1480,	1560

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