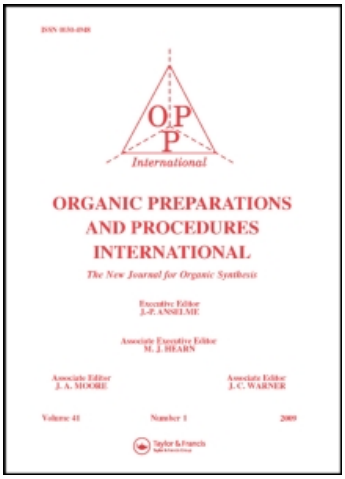

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PREPARATION OF PYRIDINE-2(1H)-THIONES FROM CHALCONES

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PREPARATION OF PYRIDINE-2(1H)-THIONES FROM CHALCONES

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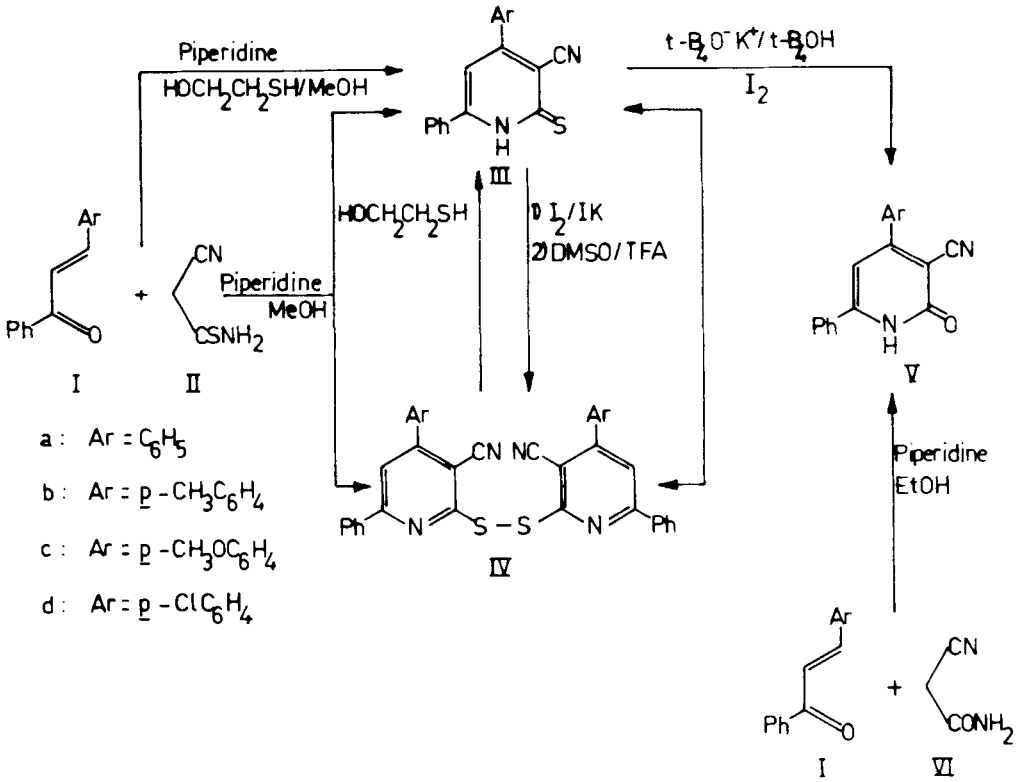
The synthesis of pyridine-2(1H)-ones from benzylideneacetophenones (chalcones) has been previously reported in this journal.[1] As far as pyridine-2(1H)-thiones are concerned, only a few major methods for their synthesis are known.[2-7]. This paper reports that the above mentioned reaction, using 2-cyanothioacetamide as the other reactant leads to the preparation of pyridine-2-(1H)-thiones together with their disulfides.

Addition of 2-cyanothioacetamide (II) to chalcones (I) takes place at room temperature in dry methanol, and is followed by cyclization and aromatization to pyridinethiones (III). Oxidative dimerization of III occurs to some extent in the reaction medium and disulfides IV are also obtained. Column chromatography allows the isolation of both compounds. However, this dimerization is prevented if the reaction is carried out in the presence of 2-mercaptoethanol, and only III is formed (Scheme I).

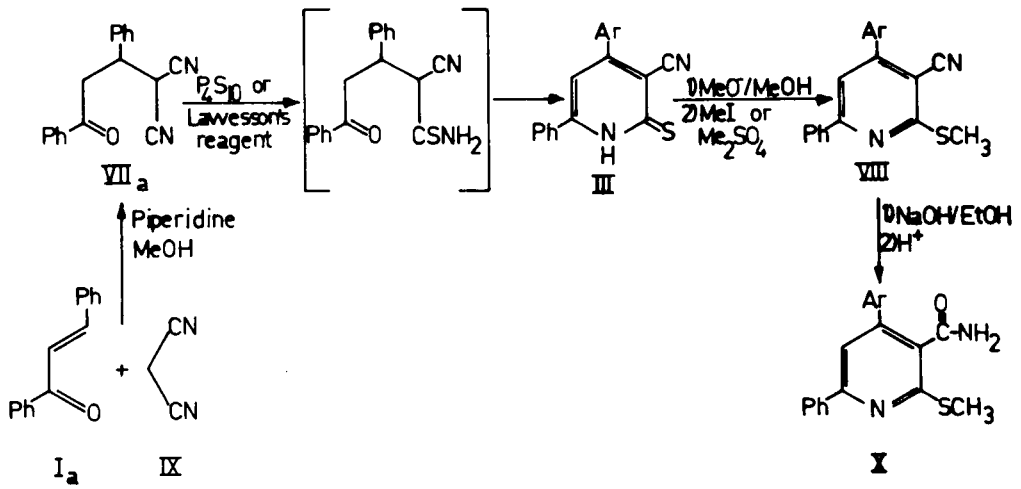


Scheme I

An alternative synthesis of pyridinethione III_a was performed, involving the generation of the thioamide group after the Michael addition. Thus, reaction of chalcone I_a with malononitrile (IX) (Scheme II) brings about the formation of an open chain adduct (VII_a)[8] which is easily isolated. Treatment of VII_a with phosphorus pentasulfide or Lawesson's reagent[9] results in the generation of a thioamide group from a nitrile group and cyclization to III_a. Pyridothione III_a can also be prepared through a Knoevenagel condensation, and subsequent spontaneous cyclization, between 2-cyanothioacetamide and dibenzoylmethane (XI_a).[10] Tables I and II summarize the physical and spectral data of compounds III,

from which a predominance of the thiocarbonyl tautomer is inferred, in agreement with previous studies.[11,12]

On the other hand, if the mixture of III and IV is treated with a suitable oxidant, such as dimethyl sulfoxide or iodine,[13] disulfides IV are isolated as the only products. Compounds IV can also be obtained by preparation of III followed by oxidation. It must be pointed out that IV_c is isolated with one molecule of acetone of crystallization. This can be eliminated by disolving the sample in benzene followed by evaporation "in vacuo". (Tables I and II).



Scheme II

Treatment of pyridine-2(1H)-thiones III with potassium tert-butoxide according to Singh's procedure[14] leads to pyridine-2(1H)-ones V, which can also be prepared from cyanoacetamide (VI) and chalcones.

Table I. Physical data of compounds III and IV

Compound	Method (a)	Time (hrs)	Yield (%)	m.p. (°C)	Elemental Analysis C	H	N	S
					%, Found (Calcd)			
IIIa	1	24	55	232[c] (HOAc)	75.00 (74.78)	4.17 (4.06)	9.72 (9.61)	11.11 (11.49)
	2a	5	68					
	2b	17	30					
IIIb	1	24	52	224-225[c] (HOAc)	75.50 (75.25)	4.63 (4.78)	9.27 (9.37)	10.60 (10.28)
IIIc	1	18	50	226-227[c] (HOAc)	71.70 (71.40)	4.40 (4.16)	8.80 (9.02)	10.06 (10.27)
IIId	1	48	48	220[c] (HOAc)	66.98 (66.63)	3.41 (3.12)	8.68 (8.88)	9.92* (10.27)
IVa	1a	20	56	248-250 (Acetone)	75.26 (75.52)	3.82 (3.85)	9.76 (10.05)	11.15 (11.55)
	1b	5	54					
IVb	1a	16	48	246 (Acetone)	75.42 (75.42)	4.35 (4.30)	9.29 (9.16)	10.64 (10.97)
IVc. Acetone.	1a	48	60	228-230[b] (Acetone)	71.09 (71.01)	4.62 (4.63)	8.09 (8.14)	9.24 (9.30)
IVd	1a	26	61	260 (Acetone)	67.18 (67.43)	3.11 (3.29)	8.71 (8.72)	9.95** (9.63)

a: See Experimental Section.

b: This compound changes its crystalline aspect at 194-196°, probably due to the loss of acetone on heating. This compound can be isolated without solvatation by dissolving it in benzene and evaporating the solvent.

c: Compounds III are stable in the solid state but dimerize slowly to IV in solution. Thus crystallization of these compound must be performed quickly and filtered as soon as the crystals appear. Otherwise, oxidative dimerization to IV takes place to some extent.

* Cl: Calcd. 11.00. Found: 11.34.

** Cl: Calcd. 11.04. Found: 11.42.

Table II. Spectral data of compounds III and IV

	NMR[1](δ)					IR[5](cm^{-1})	
Compound	N-H	Ar-H	5H	CH_3	OCH_3	N-H	CS
IIIa[2]	13.5-14.2	7.2-7.8	6.9			3150	1205
IIIb	13.3-14.3	7.1-7.8	6.9	2.3		3150	1210
IIIc	13.3-14.3	7.2-7.8			3.8	3150	1205
		6.8-7.1					
IIId	13.3-14.3	7.2-7.8	6.9			3150	1205
IVa[3]		7.3-8.1					
IVb		7.2-8.0		2.4			
IVc[4].Acetone.		7.2-8.0		2.2	3.9		
IVd		7.2-7.9					

1) All NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard.

2) Mass spectrum of IIIa: m/e=288(M^+,100), 287(60), 255(9), 244(8), 228(5), 227(8), 144(10), 140(7) and 77(9).

3) Mass spectrum of IVa: m/e=575(M^+,34), 574(78), 573(100), 509(14), 302(16), 289(17), 288(71), 287(59), 255(15), 228(11), 227(25), 140(11) and 77(18).

4) Mass spectrum of IVc: m/e=635(M^+,12), 634(24), 633(26), 331(19), 319(26), 318(100), 317(56), 303(13), 288(11), 287(24), 274(14), 241(12) and 37(12).

5) CN stretching bands appear at 2220 cm^{-1} in all cases.

Methylation of pyridinethiones III with dimethyl sulphate or methyl iodide affords methylthiopyridines VIII in good yields (Tables III and IV). Attempts to transform VIII into pyridinones V by means of alkaline hydrolysis lead to 3-carboxamido-2-methylthiopyridines (X) as the main reaction product. Compounds V are formed in trace amounts and can be identified by analytical TLC by comparison with authentic samples.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ^{1}H-NMR spectra were recorded at 60 MHz on a Varian T-60A and IR spectra were measured with a Perkin-Elmer 257 in potassium bromide pellets. A Varian MAT-711 was used for the recording of mass spectra at 100 eV. Microanalysis were performed by Centro Nacional de Química Orgánica de Madrid. The reactions and purity of compounds were monitored by TLC, performed on silica gel plates (Merck) and using ethyl acetate or benzene/ethyl acetate 4:1 Or 6:1 as the eluent. Malononitrile was obtained from Merck and used without further purification. Cyanothioacetamide (II) was prepared from malononitrile and hydrogen disulfide according to the method reported by Howard.[15] Benzylideneacetophenone (IIa) was obtained from Merck, and the remaining benzylideneacetophenones (IIb-d) were prepared by condensation of aromatic aldehydes[16-18] with acetophenone following known procedures. 3,5-Diphenyl-2-cyano-5-oxopentanonitrile (VII) was prepared as previously described.[8] Lawesson's reagent was obtained from anisole and phosphorus pentasulphide.[9]

4,6-Diaryl-3-cyanopyridine-2(1H)-thiones (III). General Procedures.

Method 1.- To a solution of benzylidene acetophenone (I) (0.011 mole) in dry methanol (20 ml) was added a solution of 2-cyanothioacetamide (0.013 mole) in dry methanol (20 ml), a few drops of piperidine and 2-mercaptoethanol (0.0015 mole) sequentially. The reaction mixture was kept at room temperature and under magnetic stirring during a variable number of

hours (see Table I). The yellow precipitate was filtered off and washed with ethanol and recrystallized from acetic acid (cooling the solution was neccesary in order to get a rapid crystallization and avoid the dimerization of III. In fact, disulfide IV was recovered from the mother liquors.

Method 2.-

a) 3,5-Diaryl-2-cyano-5-oxopentanonitrile (VII) (0.0036 mole) were dissolved in carbon disulfide (50 ml) and phosphorus pentasulfide (0.0015 mole) and triethylamine (0.0024 mole) were then added. The reaction was stirred at room temperature under nitrogen for five days. The solvent was decanted and the residue was suspended in hot ethanol and collected by filtration after cooling. The solid obtained was recrystallized from acetic acid.

b) A solution of Lawesson's reagent[9] (0.0022 mole) in a small amount of dry toluene was added to a solution of 3,5-diaryl-2-cyano-5-oxopentanonitrile (VII) (0.0036 mole) in dry toluene (20 ml). The reaction was heated at reflux temperature (under nitrogen) for 17 hr. Then the reaction mixture was cooled to room temperature and the yellow solid obtained was filtered off, washed with ethanol and recrystallized from acetic acid.

The physical and spectral data of compounds III are collected in Tables I and II.

2,2'-Bis-(4,6-diaryl-3-cyanopyridyl) disulfides (IV). General Procedure.- Benzylideneacetophenones (I) (0.022 mole) were dissolved in dry methanol (ca. 50 ml) and a solution of cyanothioacetamide (II) (0.022 mole) in dry methanol (25 ml) was added to the formed solution. A few drops of piperidine

Table III. Physical data of compounds VIII and X

Compound	Method	Time (hrs)	Yield (%)	m.p. (°C)	Elemental Analysis			
					C	H	N	S
					%, Found (Calcd)			
VIIIa	1	2	85	156-158[a]	75.50	4.63	9.27	10.59
	2	2	90		(75.35)	(4.65)	(9.37)	(11.00)
VIIIb	1	2	76	153-154[a]	75.95	5.06	8.86	10.12
					(75.83)	(5.13)	(8.86)	(10.50)
VIIIc	1	2	65	163[a]	72.29	4.82	8.43	9.64
					(72.29)	(4.95)	(8.64)	(9.91)
VIIId	1	2	88	238-240[b]	67.76	3.86	8.32	9.51*
					(68.19)	(3.85)	(8.07)	(9.73)
Xa		20	70	216-218[a]	71.25	5.00	8.75	10.00
					(71.36)	(5.29)	(8.41)	(9.80)
Xb		24	71	203[a]	71.85	5.38	8.38	9.58
					(72.15)	(5.06)	(8.40)	(9.67)
Xc		24	87	220[a]	68.57	5.14	8.00	9.14
					(68.43)	(5.37)	(8.07)	(9.52)
Xd		29	53	226-227[a]	64.32	4.23	7.90	9.03
					(64.43)	(4.40)	(7.76)	(9.45)

* Cl : Calcd. 10.55. Found : 10.84

a) From ethanol ; b) From acetone

Table IV. Spectral data of Compounds VIII and X

	NMR[1](δ)				IR[4](cm^{-1})	
Compound	Ar-H,NH_2	SCH_3	CH_3	OCH_3	ν(NH)	ν(CO)-δ(NH)
VIIIa[2]	7.1-8.1	2.70				
VIIIb	7.2-8.2	2.70	2.40			
VIIIc	6.8-8.2	2.70		3.86		
VIIId	7.1-8.1	2.70				
Xa	7.3-8.3	2.70			3390-3180	1635
Xb[3]	7.2-8.3	2.70	2.36		3380-3170	1640 1630
Xc	6.9-8.3	2.70			3380-3190	1630
Xd	7.1-8.1	2.60			3450-3170	1640

1) NMR spectra of compounds VIII were recorded in deuteriochloroform and spectra of compounds X were recorded in DMSO-d_6.

2) Mass spectrum of compound VIIIa: m/e=302(M^+,39), 301(100), 202(48), 201(22), 200(32), 199(25), 198(18), 101(12) and 99(10).

3) Mass spectrum of compound Xb: m/e=334(M^+,26), 318(17), 317(63), 316(14), 315(20), 301(33), 289(22), 202(100), 200(73), 199(46) and 198(27).

4) ν_{CH} 2920 cm^{-1} and ν_{CN} 2220 cm^{-1}.

were then added and the reaction mixture was stirred at room temperature for a variable number of hours (see Table I). The resulting precipitate was collected by filtration. It can then, be treated in two alternative ways:

a) The solid (1 g) was dissolved in 25 ml of dimethylsulfoxide with a few drops of trifluoracetic acid. The solid that separates after standing at room temperature for a variable number of hours was filtered off and recrystallized from acetone.

b) The solid (1 g) was dissolved in ca. 30 ml of ethanol and a small amount (30 mg) of iodine and potassium iodide was added. The reaction mixture was stirred at room temperature for 5 hours. The collected precipitate was washed with water and ethanol and recrystallized from acetone.

Physical and analytical data of compounds IV are collected in Table I and the spectral data in Table II.

4,6-Diaryl-3-cyano-2-methylthiopyridines (VIII). General Procedures.

Method 1.- 4,6-Diaryl-3-cyano-2-pyridothione (III) (0.0017 mole) was suspended in a solution of sodium methoxide (from 0.0051 mole of sodium) in methanol (25 ml). An excess methyl iodide (0.0028 mole) or dimethyl sulphate (0.0014 mole) was added to the resulting mixture. The precipitate obtained after two hours stirring at room temperature was filtered off and recrystallized from ethanol or acetone (Table III).

Method 2.- A suspension of disulfide IV (0.00033 mole) in a solution of sodium methoxide in ca. 30 ml of methanol (from 0.0009 mole of sodium) was treated with methyl iodide (0.00069

mole). After two hours, a solid separates and is collected by filtration and recrystallized.

4,6-Diaryl-3-carboxamido-2-methylthiopyridines (X). General Procedure.- To a suspension of the appropriate 4,6-diaryl-3-cyano-2-methylthiopyridine (VIII) (0.91 mmole) in 50 ml of ethanol, 16 ml of 36% aqueous hydroxyde were added. The reaction mixture was heated to reflux temperature during a variable length of time (see table). The solution was then evaporated until about half volume remains and it was then poured into cold water and neutralized with acetic acid. The corresponding compound VI was collected by filtration and purified by column chromatography on silica gel using benzene-ethyl acetate (4/1) as the eluent and recrystallization from ethanol.

Conversion of 3-cyano-4,6-diphenylpyridine-2-(1H)-thione (IIIa) into 2,2'-bis[3-cyano-4,6-diphenylpyridyl] disulfide (IVa).

Method 1.- A solution of IIIa (3.7 mmole, 1.09 g) with 30 mg of iodine and 20 mg of potassium iodide in 50 ml of dry ethanol was stirred at room temperature for 5 hours. The precipitate that separates was collected by filtration and washed with water and ethanol. Yield: 0.97 g (89%).

Method 2.- Compound IIIa (0.15 g, 0.5 mmole) was suspended in 15 ml of methylene chloride and 1 ml of 4N hydrochloric acid was adder, together with a solution of 0.053 g (0.8 mmole) of sodium nitrate in 0.5 ml of water. After two hours stirring at room temperature, the reaction mixture is extracted with methylene chloride using three 10 ml portions. The organic

layer is washed with water and dried over magnesium sulphate. Yield: 0.079 g (55%).

Conversion of 2,2'-bis[3-cyano-4,6-diphenylpyridyl] disulfide (IVa). into 3-cyano-4,6-diphenylpyridine-2(1H)-thione. (IIIa).- To a solution of 0.16 g (0.28 mmole) of IVa in 20 ml of chloroform, 0.12 g (1.6 mmole) of 2-mercaptoethanol are added and the reaction mixture is stirred at room temperature for 7 hours. The chloroform solution is then washed with water and dried over magnesium sulphate. On evaporation of the solvent, 0.15 g of IIIa are isolated and recrystallized from acetic acid. Yield: 0.15 g (93%).

Transformation of 3-cyano-4,6-diphenylpyridine-2(1H)-thione (IIIa) into 3-cyano-4,6-diphenylpyridine-2(1H)-one (Va).- Potassium t-butoxide (5 g) and 40 mg of iodine were added to a suspension of 0.23 g (1 mmole) of 3-cyano-4,6-diphenylpyrido-2-thione (IIIa) in 60 ml of t-butanol and the resulting solution was heated to reflux temperature for 48 hrs. The solvent was evaporated under vacuo and the residue was dissolved in the minimal amount of water and neutralized with acetic acid. The solution was extracted with two portions of ethyl acetate, washed with a dilute aqueous sodium thiosulphate and dried over sodium sulphate. The solid obtained on evaporation of the solvent was subjected to column chromatography on silica gel using benzene/ethyl acetate 4:1 as the eluent and recrystallized from ethanol. Yield: 0.117 g (55%), m.p. 302-304°C (lit. 302°[1]).

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