Pyridinethiones. VIII. The Aldol and Wittig Condensations of 3-Formyl-2(1*H*)-pyridones, -thiones and -selones. Preparation of New Cyanopyridones

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Condensations of 1-substituted-3-formyl-2(1*H*)-pyridones, -thiones and -selones with methyl ketones such as acetophenone give the corresponding chalcones in high yields. Geometry at the vinyl hydrogens is *E*. These chalcones can be cyclized with ethyl cyanoacetate in the presence of ammonium acetate to form new 3-cyano-2(1*H*)-pyridones. An effective "one-pot" preparation is worked out and an intermediate from the cyclization reaction is isolated. *Via* the Wittig reaction it is possible to prepare condensation products from 1-substituted-3-formyl-2(1*H*)-pyridinethiones and -selones with mainly *Z* geometry at the vinyl hydrogens.

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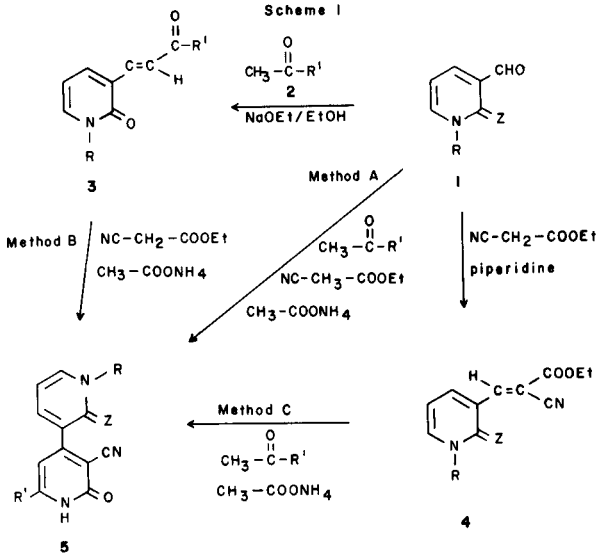
It is well known [3] that chalcones are excellent starting materials for 2(1*H*)-pyridones, in a reaction where the aldol condensation product and ethyl cyanoacetate reacts [4] in the presence of ammonium acetate.

We have recently demonstrated [5] the easy condensation of the formyl group in the 3-formyl-2(1*H*)-pyridinethiones (**1**) with compounds containing active methylene groups. This effective condensation to compounds such as **4** prompted us to investigate the related condensation of the formyl group with methyl ketones **2** such as acetophenones as well as the use of these products **3** for the preparation of a number of new 3-cyanopyridines **5**.

Scheme I



Condensation Products **3** Prepared

	Z	R	R'
3a	S	Phenyl	Phenyl
3b	S	Phenyl	4-*t*-Butylphenyl
3c	S	Phenyl	4-Chlorophenyl
3d	S	*t*-Butyl	Phenyl
3e	S	*t*-Butyl	4-Chlorophenyl
3f	S	Isopropyl	4-Chlorophenyl
3g	S	Cyclohexyl	4-Chlorophenyl
3h	S	4-Chlorophenyl	4-*t*-Butylphenyl
3i	S	4-Chlorophenyl	4-Methoxyphenyl
3j	O	Phenyl	Phenyl
3k	Se	α-Methylbenzyl	4-Chlorophenyl

Cyanopyridones **5** Prepared

	Z	R	R'	R''
5a	S	Phenyl	Phenyl	H
5b	S	Phenyl	4-Chlorophenyl	H
5c	S	Phenyl	4-Methoxyphenyl	H
5d	S	Isopropyl	Phenyl	H
5e	S	Isopropyl	4-Chlorophenyl	H
5f	S	Isopropyl	4-Methoxyphenyl	H
5g	O	Phenyl	Phenyl	H
5h	S	Phenyl	-Pentamethylene-	
5i	S	Isopropyl	-Pentamethylene-	

Starting Compounds **1** Used

	Z	R
1a	S	Phenyl [6]
1b	S	*t*-Butyl [7]
1c	S	Isopropyl [8]
1d	S	Cyclohexyl [8]
1e	S	4-Chlorophenyl [13]
1f	O	Phenyl [6]
1g	Se	α-Methylbenzyl [13]
1i	S	3-Chlorophenyl

The Condensation Products **3**.

The condensation products **3** were prepared from a methyl ketone such as an acetophenone (**2**) and a 1-substituted-3-formyl-2(1*H*)-pyridinethione (**1**) (Scheme 1). In order to examine the versatility of the reaction, some examples of the corresponding 3-formyl-2(1*H*)-pyridones and -selones were also condensed. These reactions were all performed in alcohol solvent with sodium ethoxide.

The structures of the condensation products **3** were assigned on the basis of the syntheses and analytical data. All ir spectra showed strong C=O absorption at 1660 cm^{-1}. The ^1H- and ^{13}C-nmr spectra were all very similar. In all

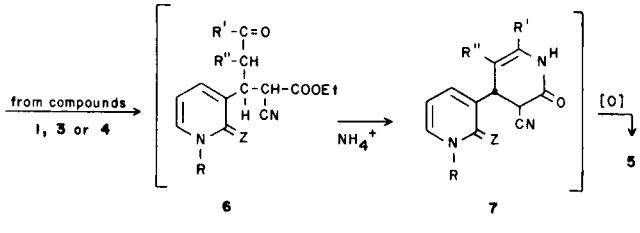
cases prepared, only the expected *E*-isomer was found, reflected in the typical *trans*-coupling constant J = 16 Hz due to the vinylic protons in the compounds **3**. Thus the large benzoyl group is always found away from the chalcogen atoms in the products **3** as depicted in Scheme 1, the most highly favoured product is the *E*-isomer [10] similar to the products of type **4** already discussed in ref [5].

The mass spectra of compounds **3** all show a small molecular ion M^+ (1%). Compounds **3** with R = aryl has a base peak corresponding to loss of benzoyl, whereas compounds **3** with R = alkyl also show loss of the aliphatic 1 substituent.

The Cyclization Reactions.

The cyclization reactions were carried out by three independent routes, (see Scheme 1). Method A is a "one pot' synthesis in which the starting formyl compound **1** is treated with a methyl ketone and ethyl cyanoacetate in ethanol in the presence of ammonium acetate, whereby the resulting pyridones **5** are obtained in high yields. However, the stepwise method which is identical to the method reported [3] previously also gives the pyridones **5** in fair yield. Method B uses the ketone condensation products **3** which are reacted with ethyl cyanoacetate and ammonium acetate whereas Method C uses the ethyl cyanoacetate condensation product [5] **4** which is reacted with a ketone and ammonium acetate. As all three methods yield the same pyridones **5** it is therefore tempting to suggest an identical intermediate **6** for all three reactions.

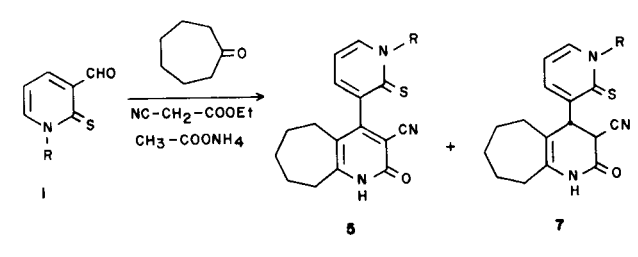
Scheme 2



Air oxidation of the dihydro derivative **7** then yields the pyridones **5**.

In a reaction with cycloheptanone as the ketone part (Method A) such a dihydro derivative **7** was actually isolated together with the expected pyridone **5**.

Scheme 3



Structure of the dihydro isomers **7** was assigned from the spectra and analyses.

The ^{1}H-nmr spectrum of **7a** and **7b** showed the coupling constants for C(3)-H and C(4)-H as $J_{3,4}$ = 2.3 Hz. Such coupling constants should normally indicate a *Z*-position of the protons. However, for related fused thiophenes similarly obtained from chalcones, van Leusen and Terpstra [15] have recently demonstrated (by X-ray) that such protons at carbons with strongly electronegative substituents in fact have the *E*-structure, with the ^{1}H-nmr coupling for these protons at 1 Hz.

On this basis we have tentatively assigned the *E*-structure for the C(3)-H relative to the C(4)-H in compounds **7** as depicted in Scheme 3.

Dihydro isomers such as **7** have been demonstrated previously [4] in the preparations of 3-cyanopyridones from the cyclization of ethyl cyanoacetate and ketones by ammonium acetate. The structure of the pyridone **5** was assigned on the basis of analytical data and spectra, thus the ir spectra showed broad bands due to a typical 2(1*H*)-pyridone NH (3300-3100 cm^{-1}) [11,12], C=O (1650 cm^{-1}) and C≡N (2225 cm^{-1}). The ^{1}H- and ^{13}C-nmr spectra were all in accord with data reported for other related pyridine derivatives [13].

Wittig Reactions.

In a previous paper [16] we have used some Wittig reaction products from the thiones **1** (Z = S) to prepare fused pyridines. In order to see if it was possible to prepare condensation products with the more versatile *Z* geometry at the vinyl hydrogens a number of Wittig reactions of **1** was carried out, Table 1 shows the results.

Scheme 4

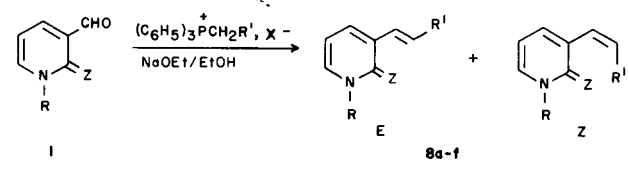


Table 1

Starting Material		Product	R'	Z	*E/Z* (in % of *E*)
1a	**8a**	Phenyl	cyano	S	11% *E*
1d	**8b**	Cyclohexyl	cyano	S	5% *E*
1a	**8c**	Phenyl	carbamido	S	>98% *E*
1i	**8d**	3-Chlorophenyl	formyl	S	>98% *E*
1h [13]	**8e**	*p*-Methoxyphenyl	carbamido	Se	81% *E*
1a	**8f**	Phenyl	carbomethoxy	S	20% *E*

It is seen that this method results in a mixture of *E/Z* isomers in which the *E/Z* ratio is mainly determined by the substituent R′ in the condensation products **8**. The *E/Z* ratio is calculated from the ^{1}H nmr spectra; for R = carbamido or formyl the condensation products **8** is nearly pure *E*-isomer while R′ = cyano or carboalkoxy gave a much larger amount of *Z* isomer. It is seen that the cyano moiety yields the *Z* isomer as the main product, this is in accordance with previous results [5] for condensation reactions on the thiones **1**. The thiones **1** (*Z* = S) and an example with a selone **1** (*Z* = Se) gave nearly identical results. However, the pyridones **1** (*Z* = O) did not react in the Wittig reaction, in contrast to the aldol condensation described above, which gave identical results for *Z* = O and S.

EXPERIMENTAL

Microanalyses were carried out at NOVO A/S Copenhagen. The ^{1}H- and ^{13}C- nmr spectra [14] were recorded on a JEOL-FX 60, ir spectra on a Perkin-Elmer 580 (potassium bromide used in all cases), uv spectra [14] on a Varian CARY 219 (absolute ethanol as solvent in all cases) and Mass spectra on a Varian MAT 311 A. Melting points were obtained on a Büchi-apparatus (uncorrected).

Synthesis of Vinyl Ketones **3**. Method a.

The required 3-formyl-2(1*H*)-pyridinethione (**1**) (0.01 mole) and 0.01 mole of the acetophenone was suspended in 30 ml absolute alcohol and warmed to 50°. Then 1 ml of 2 *M* sodium ethoxide in ethanol was added in one portion and the reaction mixture stirred for 1 hour at room temperature. The resulting yellow-orange precipitate was collected, washed with ether and dried.

Method b.

A 10% sodium hydroxide solution (6.5 ml) in water was added dropwise to a solution of 1.85 g (0.01 mole) **1b** and 0.01 mole of the acetophenone in 30 ml ethanol and the resulting mixture stirred for 1 hour. Collection of the yellow precipitate, washing with water and drying gave the title compounds in good yields.

E-3-(2′-Benzoylvinyl)-1-phenyl-2(1*H*)-pyridinethione (**3a**). Method a (ethanol as solvent).

This compound was obtained in a yield of 88% (2.8 g), mp 148-149° (ethanol); ir: 1652 cm^{-1} (C=O); uv: 427 nm (3.71), 343 nm (3.96), 274 nm (4.32), 246 nm (4.25 nm); ^{1}H nmr: 8.50 (d, 16 Hz, 1H), 8.3-7.3 (m, 13H), 6.95 (t, 7 Hz, 1H); ms: 317 (0.1%), 212 (100%).

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.68; H, 4.76; N, 4.41. Found: C, 75.31; H, 4.71; N, 4.18.

E-3-(2′-(4-*t*-Butylbenzoyl)vinyl)-1-phenyl-2(1*H*)-pyridinethione (**3b**). Method a (2-propanol as solvent).

This compound was obtained in a yield of 75% (2.8 g), mp 211-212° (ethanol); ir: 1660 cm^{-1} (C=O); uv: 430 nm (3.79), 343 nm (4.04), 278 nm (4.38), 242 nm (4.23); ^{1}H-nmr: 8.37 (d, 16 Hz, 1H), 8.1-7.3 (m, 12H), 6.62 (t, 7 Hz, 1H), 1.31 (s, 9H); ms: 373 (0.2%), 212 (100%).

Anal. Calcd. for $C_{24}H_{23}NOS$: C, 77.18; H, 6.21; N, 3.75. Found: C, 77.09; H, 6.26; N, 3.66.

E-3-(2′-4-Chlorobenzoyl)vinyl)-1-phenyl-2(1*H*)-pyridinethione (**3c**). Method a (2-propanol as solvent).

This compound was obtained in a yield of 90% (3.2 g), mp 175-176° (ethanol); ir 1660 cm^{-1} (C=O); uv: 432 nm (3.73) 345 nm (4.00), 277 nm (4.36); ^{1}H-nmr: 8.8-7.4 (m, 13H), 6.99 (t, 7 Hz, 1H); ms: 351 (0.1%), 212 (100%).

Anal. Calcd. for $C_{20}H_{14}ClNOS$: C, 68.28; H, 3.98; N, 3.98. Found: C, 67.93; H, 3.86; N, 4.02.

E-3-(2′-Benzoylvinyl)-1-*t*-butyl-2(1*H*)-pyridinethione (**3d**). Method b.

This compound was obtained in a yield of 81% (2.4 g), mp 148-149° (ethyl acetate); ir: 1660 cm^{-1} (C=O); uv: 415 nm (3.83), 349 nm (4.15), 274 nm (4.41); ^{1}H-nmr: 8.6-7.3 (m, 9H), 6.90 (t, 8 Hz, 1H), 2.03 (s, 9H); ms: M$^+$ not seen, 241 (3%), 225 (7%), 192 (14%), 136 (100%).

Anal. Calcd. for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.62; H, 6.46; N, 4.66.

E-3-(2′-(4-Chlorobenzoyl)vinyl)-1-*t*-butyl-2(1*H*)-pyridinethione (**3e**). Method b.

This compound was obtained in a yield of 78% (2.6 g), mp 158-160° (cyclohexane-toluene); ir: 1655 cm^{-1} (C=O); 417 nm (3.74), 350 nm (3.94), 277 nm (4.30); ^{1}H-nmr 8.34 (d, 16 Hz, 1H), 8.0-7.0 (m, 2H), 7.96 (d, 8 Hz, 2H), 7.43 (d, 8 Hz, 2H), 6.93 (d, 16 Hz, 1H), 6.64 (t, 7 Hz, 1H), 2.02 (s, 9H); ms: 331 (0.1%), 242 (0.7%), 192 (24%), 136 (100%).

Anal. Calcd. for $C_{18}H_{18}ClNOS$: C, 65.18; H, 5.18; N, 4.22. Found: C, 65.28; H, 5.49; N, 5.49.

E-3-(2′-(4-Chlorobenzoyl)vinyl)-1-isopropyl-2(1*H*)-pyridinethione (**3f**). Method a (2-propanol as solvent).

This compound was obtained in a yield of 66% (2.1 g), mp 192-194° (ethanol); ir: 1655 cm^{-1} (C=O); uv: 425 nm (3.71) 341 nm (3.94), 276 nm (4.33); ^{1}H-nmr 8.54 (d, 16 Hz, 1H), 8.3-8.2 (m, 1H), 8.15 (d, 9 Hz, 2H), 7.96 (d, 16 Hz, 1H), 7.62 (d, 9 Hz, 2H), 7.6-7.5 (m, 1H), 6.97 (t, 7 Hz, 1H), 6.33 (septet, 7 Hz, 1H), 1.41 (d, 7 Hz, 6H); ms: 317 (0.1%), 178 (100%), 136 (100%).

Anal. Calcd. for $C_{17}H_{16}ClNOS$: C, 64.24; H, 5.08; N, 4.41. Found: C, 64.03; H, 4.99; N, 4.24.

E-3-(2′-(4-Chlorobenzoyl)vinyl)-1-cyclohexyl-2(1*H*)-pyridinethione (**3g**). Method a (2-propanol as solvent).

This compound was obtained in a yield of 93% (3.3 g), mp 188-189° (2-propanol); ir: 1655 cm^{-1} (C=O); uv: 424 nm (3.75), 341 nm (3.98), 2.76 nm (4.38); ^{1}H-nmr: 8.53 (d, 16 Hz, 1H), 8.2-7.5 (m, 2H), 8.14 (d, 9 Hz, 2H), 7.94 (d, 16 Hz, 1H), 7.62 (d, 9 Hz, 2H), 6.94 (t, 7 Hz, 1H), 6.02 (m, 1H), 2.0-1.0 (m, broad, 10H); ms: 357 (0.1%), 218 (44%), 136 (100%).

Anal. Calcd. for $C_{20}H_{20}ClNOS$: C, 67.12; H, 5.63; N, 3.91. Found: C, 67.19; H, 5.56; N, 4.07.

E-3-(2′-(4-*t*-Butylbenzoyl)vinyl-1-(4-chlorophenyl)-2(1*H*)-pyridinethione (**3h**). Method a (ethanol as solvent).

This compound was obtained in a yield of 63% (2.6 g), mp 219-220° (ethanol); ir: 1665 cm^{-1} (C=O); uv; 430 nm (3.36), 3.44 nm (3.61), 276 nm (3.97), 245 (3.87); ^{1}H-nmr: 8.6-6.8 (m, 13H), 1.33 (s, 9H); ms: 407 (0.1%), 246 (100%).

Anal. Calcd. for $C_{24}H_{22}ClNOS$: C, 70.67; H, 5.40; N, 3.93. Found: C, 70.87; H, 5.36; N, 3.58.

E-3-(2′-(4-Methoxybenzoyl)vinyl)-1-(4-chlorophenyl)-2(1*H*)pyridinethione (**3i**). Method a (ethanol as solvent).

This compound was obtained in a yield of 13% (0.5 g), mp 159-162° (methanol); ir: 1658 cm^{-1} (C=O); uv: 427 nm (3.73), 337 nm (4.15), 309 nm (4.15), 272 nm (4.25), 2.41 nm (4.26); ^{1}H-nmr: 8.5-6.8 (m, 13H), 3.87 (s, 3H); ms: M$^+$ not seen 248 (38%), 246 (100%), 134 (90%).

Anal. Calcd. for $C_{21}H_{16}ClNO_2S$: C, 66.06; H, 4.19; N, 3.67. Found: C, 65.58; H, 4.11; N, 3.67.

E-3-(2′-Benzoylvinyl)-1-phenyl-2(1*H*)-pyridone (**3j**). Method a (ethanol as solvent).

This compound was obtained in a yield of 67% (2.0 g), mp 179-180° (ethanol); ir: 1660 cm^{-1} (C=O); uv: 372 nm (4.02), 267 nm (3.90), 224 nm (4.05); ^{1}H-nmr: 8.31 (d, 16 Hz, 1H), 8.1-7.4 (m, 12H), 7.72 (d, 16 Hz, 1H), 6.48 (t, 7 Hz, 1H); ms: 301 (2%), 196 (100%).

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.70; H, 5.02; N, 4.67. Found; C, 79.30; H, 4.90; N, 4.58.

E-3-(2′-(4-Chlorobenzoyl)vinyl)-1-((*RS*)-methylbenzyl)-2(1*H*)-pyridineselone (**3k**). Method a (propanol as solvent).

This compound was obtained in a yield of 63% (2.7 g), mp 115-118° (propanol); ir 1660 cm^{-1} (C=O); uv: 380 nm (3.56), 301 nm (3.79), 254 nm (4.13); ^{1}H-nmr: 8.0-7.0 (m, 15H), 1.77 (d, 6 Hz, 3H); ms: 427 (0.8%), 335 (3%), 288 (15%), 184 (24%), 105 (100%).

Anal. Calcd. for $C_{22}H_{18}ClNOSe$: C, 61.90; H, 4.22; N, 3.28. Found: C, 61.46; H, 4.28; N, 3.00.

1-(*p*-Chlorophenyl)-3-formyl-2(1*H*)-pyridinethione (**1e**).

This compound was prepared according to the method described previously, see ref [6], mp 164-165°.

Anal. Calcd. for $C_{12}H_8ClNOS$: C, 57.67; H, 3.20; N, 5.61. Found: C, 57.79; H, 3.29; N, 5.77.

Preparation of 3-Cyano-4,6-disubstituted-2(1*H*)-pyridones **5**. Method A.

Preparation by Reaction of 1-Substituted-3-formyl-2(1*H*)-pyridinethiones (**1**) With a Methyl Ketone and Ethyl Cyanoacetate in the Presence of Ammonium Acetate. General Procedure.

A solution of **1** (0.01 mole), the ketone (0.01 mole), ethyl cyanoacetate (0.01 mmole) and ammonium acetate (0.08 mole) in absolute ethanol (50 ml) was heated under reflux for 6 hours and left to cool. The separated solid was filtered and crystallized from a suitable solvent to give **5**.

Method B.

Preparation by Reaction of Compounds **3** With Ethyl Cyanoacetate in the Presence of Ammonium Acetate. General Procedure.

A solution of **3** (0.01 mole), ethyl cyanoacetate (0.01 mole) and ammonium acetate (0.08 mole) in absolute ethanol (50 ml) was heated under reflux for 6 hours and left to cool. The separated solid was filtered and crystallized from acetic acid to give **5**.

Method C.

Preparation by Reaction of 3-(2-Cyano-2-ethoxycarbonylvinyl)-1-phenyl-2(1*H*)-pyridinethione (**4**) [5] With Methyl Ketones. General Procedure.

A solution of **4** (0.01 mole), an appropriate methyl ketone (0.01 mole) and ammonium acetate (0.08 mole) in absolute ethanol (50 ml) was heated under reflux for 6 hours and left to cool. The solid obtained was filtered off and recrystallized from acetic acid to give the corresponding 3-cyano-2(1*H*)-pyridones **5**, identical with authentic samples prepared as before (ir and tlc and mixed mp).

3-Cyano-4-(1-phenyl-2(1*H*)thiopyrid-3-yl)-6-phenyl-2(1*H*)-pyridone (**5a**). Method A.

This compound was obtained in a yield of 63% (2.4 g), [Method B, yield 1.71 g (45%)] [Method C, yield 2.0 g (52%)], mp 337-338° (acetic acid); ir: 3300-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1650 cm^{-1} (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): 7.57-8.63 (m, 11H), 9.19 (t, 1H), 9.28 (d, 1H), 9.84 (d, 1H); ms: 381 (73%, M$^+$), 380 (100%), 355 (39%).

Anal. Calcd. for $C_{23}H_{15}N_3OS$: C, 72.42; H, 3.96; N, 11.02; S, 8.40. Found: C, 71.93; H, 3.87; N, 10.69; S, 7.93.

3-Cyano-4-(1-phenyl-2(1*H*)-thiopyrid-3-yl)-6-*p*-chlorophenyl-2(1*H*)-pyridone (**5b**). Method A.

This compound was obtained in a yield of 60% (2.5 g), [Method C, yield 1.99 (48%)], mp 360° (acetic acid); ir: 3300-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1640 cm^{-1} (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): 7.48-7.97 (m, 10H), 8.09 (t, 1H), 8.13 (d, 1H), 8.17 (d, 1H); ms: 415 (59% M$^+$), 414 (100%), 389 (25%).

Anal. Cald. for $C_{23}H_{14}ClN_3OS$: C, 66.42; H, 3.39; Cl, 8.52; N, 10.10; S, 7.71. Found: C, 66.90; H, 3.38; Cl, 8.58; N, 10.33; S, 7.58.

3-Cyano-4-(1-phenyl-2(1*H*)-thiopyrid-3-yl)-6-*p*-methoxyphenyl-2(1*H*)-pyridone (**5c**). Method A.

This compound was obtained in a yield of 54% (2.2 g), [Method C, yield 2.0 g (49%)], mp 333-335° (acetic acid); ir: 3350-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1650 cm^{-1} (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): 4.07 (s, 3H), 7.23-8.36 (m, 10H), 8.50 (t, 1H), 9.20 (d, 1H), 9.90 (d, 1H); ms: 411 (82% M$^+$), 410 (100%), 385 (50%).

Anal. Calcd. for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21; S, 7.79. Found: C, 69.87; H, 4.07; N, 10.08; S, 7.87.

3-Cyano-4-(1-isopropyl-2(1*H*)-thiopyrid-3-yl)-6-phenyl-2(1*H*)-pyridone (**5d**). Method A.

This compound was obtained in a yield of 63% (2.2 g), mp 288-289° (ethanol); ir: 3300-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1640 cm^{-1} (C=O); ^{1}H-nmr: 1.37 (s, 3H), 1.48 (s, 3H), 6.12-6.34 (m, 1H), 6.76 (s, 1H), 6.91-7.13 (m, 1H), 7.52-7.64 (m, 5H), 7.67-7.79 (m, 1H), 7.86-8.42 (m, 1H); ms: 347 (100% M$^+$), 304 (62%), 278 (20%).

Anal. Calcd. for $C_{20}H_{17}N_3OS$: C, 69.14; H, 4.93; N, 12.09; S, 9.23. Found: C, 69.22; H, 4.86; N, 12.02; S, 8.91.

3-Cyano-4-(1-isopropyl-2(1*H*)-thiopyrid-3-yl)-6-*p*-chlorophenyl-2(1*H*)-pyridone (**5e**). Method A.

This compound was obtained in a yield of 63% (2.4 g), mp 329-330° (ethanol); ir: 3300-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1640 cm^{-1} (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): 1.92 (s, 3H), 2.02 (s, 3H), 6.67-6.89 (m, 1H), 7.65 (s, 1H), 7.80-8.12 (m, 4H), 8.58 (t, 1H), 9.67 (d, 1H), 9.81 (d, 1H); ms: 381 (100% M$^+$), 338 (73%), 312 (23%).

Anal. Calcd. for $C_{20}H_{16}ClN_3OS$: C, 62.91; H, 4.22; Cl, 9.29; N, 11.00; S, 8.38. Found: C, 62.78; H, 4.14; Cl, 9.22; N, 11.07; S, 8.34.

3-Cyano-4-(1-isopropyl-2(1*H*)-thiopyrid-3-yl)-6-*p*-methoxyphenyl-2(1*H*)-pyridone (**5f**). Method A.

This compound was obtained in a yield of 53% (2.0 g), mp 334-335° (ethanol); ir: 3400-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1640 cm^{-1} (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): 1.91 (s, 3H), 2.02 (s, 3H), 4.07 (s, 3H), 5.43-5.64 (m, 1H), 7.37 (s, 1H), 8.07-8.22 (m, 4H), 8.30-8.55 (t, 1H), 9.32-9.42 (d, 1H), 9.64-9.79 (d, 1H); ms: 377 (100% M$^+$), 334 (48%), 308 (13%).

Anal. Calcd. for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13; S, 8.49. Found: C, 66.37; H, 5.04; N, 11.17; S, 8.37.

3-Cyano-4-(1-phenyl-2(1*H*)-oxopyrid-3-yl)-6-phenyl-2(1*H*)-pyridone (**5g**). Method A.

This compound was obtained in a yield of 63% (2.3 g) [Method B yield 1.8 g (49%), mp 345-346°] (acetic acid); ir: 3300-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1650 cm^{-1} (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): 7.41-8.13 (m, 11H), 8.33-8.56 (t, 1H), 9.03-9.13 (d, 1H), 9.79-9.92 (d, 1H); ms: 365 (100% M$^+$), 364 (53%).

Anal. Calcd. for $C_{23}H_{15}N_3O_2$: C, 75.60; H, 4.17; N, 11.50. Found: C, 75.46; H, 4.07; N, 11.50.

3-Cyano-4-(1-phenyl-2(1*H*)-thiopyrid-3-yl)-5,6-pentamethylene-2(1*H*)-pyridone (**5h**) and 3-Cyano-4-(1-phenyl-2(1*H*)-thiopyrid-3-yl)-5,6-pentamethylene-3,4-dihydro-2(1*H*)-pyridone (**7a**).

Method A was applied using cyclopentanone as the ketone. The product (2.6 g) was subjected to preparative tlc on silica gel 60 HF 254 (Merck) and developed with a mixture of chloroform and methanol (9:1). Extraction (methanol) of the lower band (R_F 0.58) followed by evaporation *in vacuo* afforded **5h** (1 g, 28%) as yellow crystals, mp 344-345° (methanol); ir: 3350-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1645 cm^{-1} (C=O); ^{1}H-nmr: 1.63-2.47 (m, 10H), 6.86-7.09 (t, 1H), 7.29-7.62 (m, 6H), 8.09-8.23 (d, 1H); ms: 373 (80% M$^+$), 330 (100%).

Anal. Calcd. for $C_{22}H_{19}N_3OS$: C, 70.75; H, 5.13; N, 11.25. Found: C, 70.28; H, 5.57; N, 11.11.

The upper band (R_F 0.74) on extraction yielded **7a** (1.3 g, 33%) as yellow crystals, mp 243-244° (methanol); ir: 3300-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1690 cm^{-1} (C=O); ^{1}H-nmr: 1.66-2.49 (m, 10H), 4.49 (d, 1H, J = 2.3 Hz), 4.65 (d, 1H, J = 2.3 Hz), 6.36-6.97 (t, 1H), 7.04-7.96 (m, 5H), 8.03-8.13 (d, 1H), 9.59-9.78 (d, 1H); ms: 375 (100% M$^+$), 342 (52%), 200 (86%).

Anal. Calcd. for $C_{22}H_{21}N_3OS$: C, 70.37; H, 5.64; N, 11.19; S, 8.54. Found: C, 70.47; H, 5.72; N, 11.12; S, 8.53.

3-Cyano-4-(1-isopropyl-2(1*H*)-thiopyrid-3-yl)-5,6-pentamethylene-2(1*H*)-pyridone **5i** and 3-Cyano-4-(1-isopropyl-2(1*H*)-thiopyrid-3-yl)-5,6-pentamethylene-3,4-dihydro-2(1*H*)-pyridone (**7b**).

Method A was applied using cycloheptanone as the ketone. The product (2.4 g) was subjected to preparative tlc on silica gel 60 HF 254 (Merck), and then developed with a mixture of chloroform and methanol (9:1). Extraction (methanol) of the lower band (R_F 0.57) followed by evaporation *in vacuo* afforded **5i** (0.8 g, 24%) as yellow crystals, mp 340-341° (methanol); ir 3350-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1645 cm^{-1} (C=O); ^{1}H-nmr: 1.35 (s, 3H), 1.46 (s, 3H), 1.63-2.50 (m, 10H), 5.96-6.31 (m, 1H), 6.42-6.98 (t, 1H), 7.35-7.49 (d, 1H), 8.28-8.41 (d, 1H), 12.41 (s, 1H, NH); ms: 39 (51% M$^+$), 296 (100%).

Anal. Calcd. for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.23; N, 12.38; S, 9.44. Found: C, 66.93; H, 6.25; N, 12.29; S, 9.56.

The upper band (R_f 0.77) on extraction yielded **7b** (1.2 g, 36%) as pale yellow crystals, mp 241-242° (methanol); ir: 3300-3100 cm^{-1} br (NH), 2220 cm^{-1} (CN), 1690 cm^{-1} (C=O); ^{1}H-nmr: 1.34 (s, 3H), 1.46 (s, 3H), 1.65-2.38 (m, 10H), 3.93 (d, 1H, J = 2.3 Hz), 4.56 (d, 1H, J = 2.3 Hz), 6.21-6.43 (m, 1H), 6.82-7.05 (t, 1H), 7.25-7.35 (d, 1H), 8.25-8.34 (d, 1H), 9.74 (s, 1H, NH); ms: 341 (30% M$^+$), 298 (100%).

Anal. Calcd. for $C_{19}H_{23}N_3OS$: C, 66.83; H, 6.79; N, 12.31; S, 9.39. Found: C, 66.83; H, 6.83; N, 12.25; S, 9.56.

Preparation of 3-Vinylpyridines **8** (Wittig Reactions). General Procedure.

The appropriate phosphonium salt (0.01 mole) was stirred in absolute ethanol (30 ml) whereupon sodium ethoxide in ethanol was added (5 ml, 2 *M*). After 10 minutes the appropriate aldehyde **1** (0.01 mole) was added. The reaction was followed by tlc and the precipitate isolated when the starting material was consumed. The precipitate was stirred with water (50 ml) for 30 minutes. Filtering and drying yielded the yellow crystalline products **8**.

3-(2-Cyanovinyl)-1-phenyl-2(1*H*)-pyridinethione (**8a**).

This compound was obtained in a yield of 83% (2.0 g), mp 140-143° (2-propanol); ir: 2205 cm^{-1} (CN); uv: 421 nm (3.62), 324 nm (4.01), 242 nm (4.42), 213 nm (4.26); ^{1}H-nmr: 8.3-7.4 m (H-4, H-6, H-7, phenyl-H), 7.01 (t, 6.9 Hz, H-5), 6.50 (d, 14.8 Hz, *"E"* H-8), 5.96 (d, 11.7 Hz, *"Z"* H-8); ^{13}C-nmr: 179.0 ppm (C-2); ms: 238 (14% M$^+$), 137 (60%), 136 (100%), 111 (31%).

Anal. Calcd. for $C_{14}H_{10}N_2S$: C, 70.59; H, 4.20; N, 11.76; S, 13.45. Found: C, 70.52; H, 4.21; N, 11.79; S, 13.50.

3-(2-Cyanovinyl)-1-cyclohexyl-2(1*H*)-pyridinethione (**8b**).

This compound was obtained in a yield of 60% (1.5 g), mp 148-150° (2-propanol); ir: 2210 cm^{-1} (CN); uv: 408 nm (3.23), 325 nm (3.42), 242 nm (3.57), 213 nm (3.64); ^{1}H-nmr: 8.37 (dd, 1.4 Hz, 6.7 Hz, H-6), 7.85 (dd, 1.4 Hz, 6.7 Hz, H-4), 7.72 (d, 11.8 Hz, H-7), 7.00 (t, 6.7 Hz, H-5), 5.91 (d, 11.8 Hz, H-8), 5.90 (m, α-H in cyclohexyl), 2.0-1.0 (m, rest of cyclohexyl); ^{13}C-nmr: 176.8 ppm (C-2); ms: 244 (45% M$^+$), 163 (100%), 161 (55%), 136 (35%).

Anal. Calcd. for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46; S, 13.12. Found: C, 69.16; H, 6.61; N, 11.48; S, 12.82.

3-(Carbamidovinyl)-1-phenyl-2(1*H*)-pyridinethione (**8c**).

This compound was obtained in a yield of 48% (1.2 g), mp 240-243° (ethoxyethanol); ir: 3340 cm^{-1} br (NH), 1664 cm^{-1} (C=O); uv: 410 nm (3.65), 325 nm (4.06), 239 nm (4.33), 211 nm (4.35); ^{1}H-nmr: 8.07 (dd, 1.4 Hz, 7.5 Hz, H-6), 8.10 (d, 16.0 Hz, H-7), 7.83 (dd, 1.4 Hz, 7.5 Hz, H-4), 7.6-7.4 (m, phenyl-H), 7.3 (S br, NH_2), 6.88 (t, 7.9 Hz, H-9), 6.52 (d, 16.0 Hz); ^{13}C-nmr: 176.8 ppm (C-2), 166.0 ppm (C-amide); ms: 256 (3% M$^+$), 212 (100%).

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 11.06; S, 12.46. Found: C, 65.29; H, 4.65; N, 11.06; S, 12.46.

3-(2-Formylvinyl)-1-(3-chlorophenyl)-2(1*H*)-pyridinethione (**8d**).

Formylmethylenetriphenyl phorphorane [17] (3.60 g, 0.0118 mole) and 2.95 g of **1** (0.0118 mole) was refluxed in 50 ml benzene (dry) for 1 hour. Standing (5°) overnight yielded 1.8 g (65%) of a yellow powder, mp 202-203° (ethyl acetate-hexane); ir: 1697 cm^{-1} (C=O); uv: 431 nm (3.63), 335 nm (4.01), 245 nm (4.28); ^{1}H-nmr: 9.72 (d, 7.7 Hz, formyl H), 8.35 (d, 16.2 Hz, H-7), 8.3-7.3 (m, H-4, H-6, phenyl-H), 6.94 (t, 7.0 Hz, H-5), 6.81 (dd, 7.7 Hz, 16.2 Hz, H-8); ^{13}C-nmr: 193.9 ppm (formyl-C), 179.7 ppm (C-2); ms: 275 (1%, M$^+$), 248 (36%), 246 (100%), 135 (13%).

Anal. Calcd. for $C_{16}H_{10}ClNOS$: C, 60.98; H, 3.63; N, 5.08. Found: C, 60.98; H, 3.63; N, 5.15.

3-(Carbamidovinyl)-1-(4-methoxyphenyl)-2(1*H*)-pyridineselone (**8e**).

This compound was obtained in a yield of 75% (2.5 g), mp 258-260° (2-methoxyethanol); ir: 3360 cm^{-1} br (NH), 1671 cm^{-1} (C=O); uv: 429 nm (3.62), 351 nm (4.08), 242 nm (4.32), 219 nm (4.48); ^{1}H-nmr: 8.22 (d, 6.3 Hz, H-6), 8.14 (d, 15.9 Hz, *"E"* H-7), 7.79 (d, 7.2 Hz, H-4), 7.5-6.8 (m, H-5 *"Z"* H-7, phenyl-H, NH_2), 6.41 (d, 15.9 Hz, *"E"* H-8), 5.99 (d, 12.1 Hz, *"Z"* H-8), 3.82 (s, O-CH_3); ^{13}C-nmr: 178.9 ppm (C-Z), 165.9 ppm (C=O).

Anal. Calcd. for $C_{15}H_{14}N_2O_2Se$: C, 54.06; H, 4.23; N, 8.41. Found: C, 53.80; H, 4.30; N, 8.21.

3-(2-Carbomethoxyvinyl)-1-phenyl-2(1*H*)-pyridinethione (**8f**).

This compound was obtained in a yield of 89% (2.4 g), mp 142-144° (ethanol); ir: 1715 cm^{-1} (*"Z"* C=O), 1698 cm^{-1} (*"E"* C=O); uv: 400 nm (3.61), 324 nm (4.00), 234 nm (4.18); ^{1}H-nmr: 8.17 (d, 16.5 Hz, *"E"* H-7), 7.93 (d, 7.0 Hz, H-6), 7.65 (d, 7.0 Hz, H-4), 7.36 (m, phenyl-H), 7.17 (12.2 Hz, *"Z"* H-7), 6.82 (t, 7.1 Hz, H-5), 6.53 (d, 16.5 Hz, *"E"* H-8), 6.03 (d, 12.2 Hz *"Z"* H-8), 3.72 (s, *"E"* OCH_3), 3.62 (s, *"Z"* OCH_3); ^{13}C-nmr: 178.0 ppm (C-Z), 165.8 ppm (*"E"* C-9), 165.1 ppm (*"Z"* C-9); ms: 271 (13% M$^+$), 212 (100%).

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.81. Found: C, 66.01; H, 4.80; N, 5.07; S, 11.56.

3-Formyl-1-(3-chlorophenyl)-2(1*H*)-pyridinethione (**1i**).

This compound was prepared as described in ref [6], orange crystals (67%), mp 195-197° (2-butanone).

Anal. Calcd. for $C_{12}H_8ClNOS$: C, 57.72; H, 3.23; N, 5.61. Found: C, 57.77; H, 3.30; N, 5.61.

3-Formyl-1-(4-chlorophenyl)-2(1*H*)-pyridinethione (**1e**).

This compound was prepared as described in ref [6], orange crystals (85%), mp 164-165° (2-propanol).

Anal. Calcd. for $C_{12}H_8ClNOS$: C, 57.72; H, 3.32; N, 5.61. Found: C, 57.79; H, 3.29; N, 5.77.

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