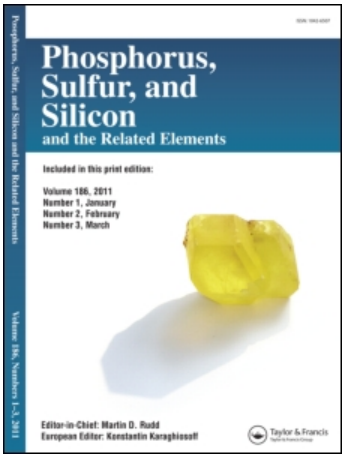


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHETIC ROUTE TO FURYL- AND THIENYL-SUBSTITUTED PYRIDINE DERIVATIVES

Galal Eldin Hamza Elgemeie[a]; Hussein Fouad Zohdi[b]; Sherif Mourad Sherif[b]
[a] Chemistry Department, Faculty of Science, Bani Suef, Egypt [b] Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

To cite this Article Elgemeie, Galal Eldin Hamza , Zohdi, Hussein Fouad and Sherif, Sherif Mourad(1990) 'ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHETIC ROUTE TO FURYL- AND THIENYL-SUBSTITUTED PYRIDINE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 54: 1, 215 — 219
To link to this Article: DOI: 10.1080/10426509008042141
URL: http://dx.doi.org/10.1080/10426509008042141

Phosphorus, Sulfur, and Silicon, 1990, Vol. 54, pp. 215–219
Reprints available directly from the publisher
Photocopying permitted by license only

Communication

ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHETIC ROUTE TO FURYL- AND THIENYL-SUBSTITUTED PYRIDINE DERIVATIVES

GALAL ELDIN HAMZA ELGEMEIE†
Chemistry Department, Faculty of Science, Bani Suef, Egypt

and

HUSSEIN FOUAD ZOHDI and SHERIF MOURAD SHERIF
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

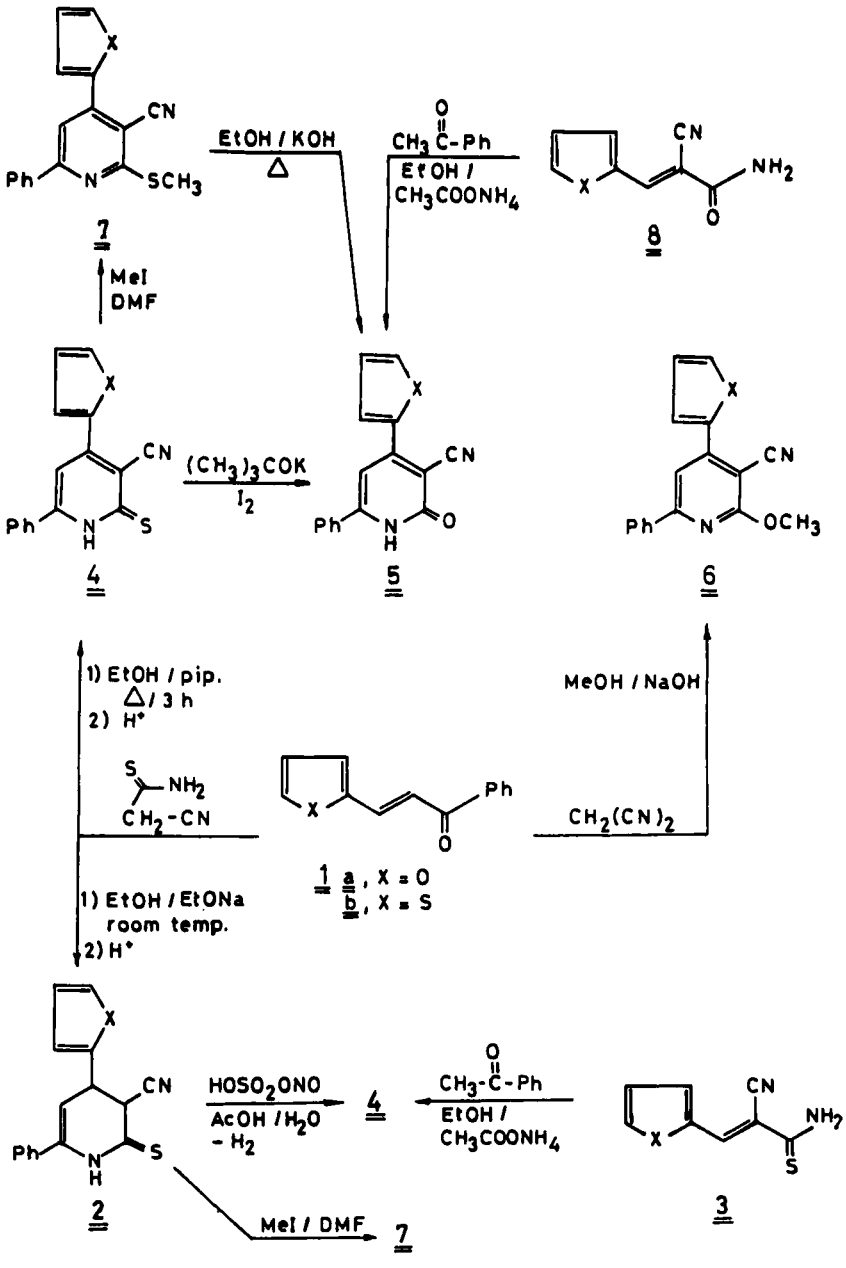
(Received November 8, 1989; in final form March 6, 1990)

A novel synthesis of 2-thio-, and 2-oxo- and 2-methoxy-3-cyano-pyridine derivatives utilizing 2-furylmethylene- and 2-thienylmethylene derivatives of acetophenone and activated nitriles as starting components is described.

INTRODUCTION

Activated nitriles are highly reactive reagents that have been extensively utilized in heterocyclic synthesis.[1–3] As a part of our program directed toward development of new simple and efficient procedures for the synthesis of pyridines of potentially synthetic value,[4,5] we have recently reported a new procedure for synthesis of pyridine-2(**1H**)-thiones via the reaction of arylmethylenecyanothioacetamide with active methylene reagents.[6,7] The importance of the synthesized compounds as intermediates for the synthesis of the biologically active deaza and folic acid ring system, prompted our interest in the synthesis and chemistry of this class of compounds.[8]

In the present paper we report reactions of 2-furylmethylene- and 2-thienylmethylene-acetophenones *1* with activated nitriles and related reactions for the synthesis of several substituted pyridine derivatives by different synthetic routes. Moreover, the results of our work aimed to define the scope and limitation of our procedure for the synthesis of pyridine derivatives is also reported. Thus, it has been found that *1* reacts with cyanothioacetamide in refluxing ethanol containing catalytic amounts of piperidine to give the pyridine-2(**1H**)-thione derivatives *4*, whereas the corresponding dihydropyridinethiones *2* were obtained from the reaction conducted at room temperature in presence of sodium ethoxide. Structures of *4* were established based on elemental analyses and spectral data (ms, ir and ^{1}H nmr, cf. Tables I and II). The formation of *4* from *1* and cyanothioacetamide can be explained by condensation involving Michael-type addition of the methylene function in cyanothioacetamide to the activated double bond in *1* to yield the



dihydropyridine *2* and subsequent dehydrogenation of *2*. Methylthiopyridines *7* resulted from treatment of *4* or *2* with methyl iodide in dimethylformamide-potassium hydroxide. Hydrolysis of *7* with potassium hydroxide in ethanol led to the 2-oxo-3(**1H**)-pyridinecarbonitriles *5*, which were also formed in good yield from the reaction of 2-furylmethylene- and 2-thienylmethylene-cyanoacetamide *8* with acetophenone in ethanol-ammonium acetate, and the reaction of *4* with iodine and potassium tert-butoxide.

The methoxypyridine derivative of compound *5* can be prepared by treating the chalcone *1* with malononitrile in MeOH-NaOH. Structure *6* was established based on elemental analysis and spectral data (ms, ir, ^{1}H nmr, cf. Tables I and II). The formation of *6* from *1* and malononitrile provides a new route for the synthesis of the difficultly accessible alkoxypyridine derivatives. The dihydropyridinethiones *2* were oxidised by heating in acetic-nitrosylsulfuric acid to give the pyridine-2(**1H**)-thiones *4*. Compounds *4* could also be prepared by the reaction of 2-furylmethylene- and 2-thienylmethylene-cyanothioacetamide *3* with acetophenone in ethanol-ammonium acetate.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were obtained (KBr) on a Pye Unicam Spectra-1000 spectrophotometer or on a Shimadzu IR 200. ^{1}H nmr spectra were measured on a Varian EM 390-90 MHz in DMSO using TMS as internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the analytical data unit at Cairo University.

Compounds *1*, *3* and *8* were prepared following literature procedure.[9,10]

4-Substituted 3-cyano-3,4-dihydro-6-phenylpyridine-2(1H)-thiones (2a,b). General Procedure: A mixture of the chalcone *1* (0.01 mol), cyanothioacetamide (0.01 mol) and NaOEt (0.01 mol) in absolute EtOH (30 ml) was stirred for 2 h at room temperature. The reaction mixture was poured slowly into ice/water, acidified with cold dilute HCl. The precipitated solid was collected by filtration, washed with water and crystallized from EtOH (cf. Table 1).

4-Substituted 3-cyano-6-phenylpyridine-2(1H)-thiones (4a,b). Method a: A mixture of *1* (0.01 mol) and cyanothioacetamide (0.01 mol) was dissolved in EtOH (30 ml), a few drops of piperidine were

TABLE I

List of compounds *2a,b–7a,b*

Compound*	Solvent of Cryst.	m.p.(°C)	Yield** (%)	Mol. Formula	Found / Calcd C	(%) H	N
2a	EtOH	166	72	$C_{16}H_{12}N_2OS$	68.9 68.6	4.8 4.3	9.6 10.0
2b	EtOH	172	84	$C_{16}H_{12}N_2S_2$	65.2 64.9	4.4 4.1	9.1 9.5
4a[1]	EtOH-DMF	218–20	68[a]	$C_{16}H_{10}N_2OS$	68.8 69.1	4.0 3.6	9.8 10.1
4b	EtOH-DMF	234–36	70[a]	$C_{16}H_{10}N_2S_2$	65.8 65.3	3.8 3.4	9.3 9.5
5a	dioxane	294–96	55[a]	$C_{16}H_{10}N_2O_2$	73.0 73.3	4.1 3.8	10.5 10.7
5b[2]	EtOH	280–82	50[a]	$C_{16}H_{10}N_2OS$	68.8 69.1	4.0 3.6	9.7 10.1
6a[3]	MeOH	142	48	$C_{17}H_{12}N_2O_2$	73.6 73.9	4.0 4.3	9.7 10.1
6b[4]	EtOH	146	52	$C_{17}H_{12}N_2OS$	70.1 69.9	4.4 4.1	9.3 9.6
7a[5]	EtOH	140	66[a]	$C_{17}H_{12}N_2OS$	69.5 69.9	4.0 4.1	10.0 9.6
7b	MeOH	134	60[a]	$C_{17}H_{12}N_2S_2$	65.8 66.2	4.2 3.9	9.5 9.1

* [1]M^+ = 278; [2]M^+ = 278; [3]M^+ = 276; [4]M^+ = 292; [5]M^+ = 292.

** [a]method a (cf. Experimental).

TABLE II

Spectroscopic data for the compounds listed in Table 1

Compound	IR (cm^{-1}) (Selected bands)	^1H NMR (δ ppm)
*2a**	2210 (CN); 3240 (NH)	4.23 (d, J = 6.0 Hz, 1H, pyridine 4-H); 4.88 (d, J = 4.5 Hz, 1H, pyridine 3-H); 6.1 (d, J = 5.5 Hz, 1H, pyridine 5-H); 7.1–8.0 (m, 8H, C_6H_5 and furan 3,4,5-H); 12.02 (s, br, 1H, NH)
4a	2215 (CN); 3380 (NH)	6.72 (m, 1H, furan 4-H); 7.00 (s, 1H, pyridine 5-H); 7.32–7.99 (m, 7H, C_6H_5 and furan 3,5-H); 13.98 (s, br, 1H, NH)
4b	2220 (CN); 3280 (NH)	7.05 (s, 1H, pyridine 5-H); 7.24 (m, 1H, thiophen 4-H); 7.38–7.88 (m, 6H, C_6H_5 and thiophen 3-H); 8.00 (m, 1H, thiophen 5-H); 14.00 (s, br, 1H, NH)
5a	2220 (CN); 3300 (NH); 1690 (CO)	6.78 (m, 1H, furan 4-H); 7.00 (s, 1H, pyridine 5-H); 7.42–7.88 (m, 6H, C_6H_5 and furan 3-H); 7.94 (s, 1H, furan 5-H); 12.45 (s, br, 1H, NH)
5b	2225 (CN); 3350 (NH); 1685 (CO)	7.02 (s, 1H, pyridine 5-H); 7.26–7.92 (m, 8H, C_6H_5 and thiophen 3,4,5-H); 12.30 (s, br, 1H, NH)
6a	2220 (CN)	4.00 (s, 3H, OCH_3); 6.82 (m, 1H, furan 4-H); 7.20–7.92 (m, 6H, C_6H_5 and pyridine 5-H); 8.02 (m, 2H, furan 3,5-H)
6b	2220 (CN)	3.99 (s, 3H, OCH_3); 7.22 (m, 1H, thiophen 4-H); 7.42 (m, 3H, phenyl protons); 7.50 (s, 1H, pyridine 5-H); 7.85 (m, 2H, phenyl protons); 8.08 (m, 2H, thiophen 3,5-H)
7a	2210 (CN)	2.61 (s, 1H, SCH_3); 6.72 (m, 1H, furan 4-H); 7.33–7.70 (m, 4H, phenyl protons and pyridine 5-H); 7.92 (m, 2H, phenyl protons); 8.1 (m, 2H, furan 3,5-H)
7b	2220 (CN)	2.58 (s, 1H, SCH_3); 7.02 (m, 1H, thiophen 4-H); 7.20–7.85 (m, 6H, C_6H_5 and pyridine 5-H); 8.00 (m, 2H, thiophen 3,5-H)

* Exists in the form of cis and trans stereoisomers (ratio 1:1, interconvertable).

then added. The mixture was refluxed for 3 h. The precipitated solid product was filtered off and crystallized from EtOH-DMF (cf. Table I).

Method b: To a suspension of 0.01 mol of *2* in AcOH (30 ml), nitrosylsulfuric acid (5 ml, prepared from 0.7 g $NaNO_2$, 9.4 ml H_2SO_4 and 2 ml H_2O) was added. The mixture was heated under reflux for 30 min., and then cooled. The resulting solid was collected and crystallized from EtOH-DMF.

Method c: A mixture of *3* (0.01 mol) and acetophenone (0.01 mol) was dissolved in ethanol (30 ml), ammonium acetate (0.015 mol) was then added. The mixture was refluxed for 3 h. The precipitated solid produce was filtered off and crystallized from EtOH-DMF.

4-Substituted 3-cyano-6-phenylpyridine-2(1H)-ones (5a,b). Method a: Compound *7* was suspended in EtOH (30 ml) and 30% aqueous KOH (10 ml) was added. The mixture was heated to reflux for 1 h and then was poured into cold water and acidified with AcOH. The resulting solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

Method b: To a solution of *4* (0.01 mol) in 30 ml tert-butanol, $(CH_3)_3COK$ (0.03 mol) and iodine (0.5 g) were added. The resulting solution was refluxed for 48 h, cooled, evaporated in vacuo and then neutralized with cold dilute HCl. The resulting residue was triturated with ethanol to give a solid product which was collected by filtration and crystallized from the proper solvent.

Method c: A mixture of *8* (0.01 mol) and acetophenone (0.01 mol) was dissolved in ethanol (30 ml), ammonium acetate (0.015 mol) was then added. The mixture was refluxed for 3 h. The precipitated solid product was filtered off and crystallized from the proper solvent.

4-Substituted 3-cyano-2-methoxy-6-phenylpyridines (6a,b). General Procedure: A mixture of *1* (0.01 mol), malononitrile (0.01 mol) was dissolved in MeOH (30 ml), NaOH (0.01 mol) was then added.

The mixture was refluxed for 2 h. The precipitated solid product was filtered off and crystallized from the proper solvent (cf. Table I).

4-Substituted 3-cyano-2-methylthio-6-phenylpyridines (7a,b). Method a: A mixture of *4* (0.01 mol), KOH powder (0.01 mol), and MeI (0.02 mol) in dry DMF (30 ml) was stirred at room temperature for 3 h, then diluted with cold water (100 ml). The resulting solid product was collected by filtration and crystallized from the proper solvent (cf. Table 1).

Method b: A mixture of *2* (0.01 mol), KOH powder (0.01 mol), and MeI (0.02 mol) in dry DMF (30 ml) was heated at 100°C for 2 h, cooled to room temperature, poured into 80 ml of H_2O, and filtered. The collected solid was crystallized from the proper solvent.

REFERENCES

1. G. E. H. Elgemeie and F. A. M. A. Aal, *Heterocycles*, **24,** 349 (1986).
2. G. E. H. Elgemeie, H. A. Elfahham, S. Elgamal and M. H. Elnagdi, *Heterocycles*, **23,** 1999 (1985).
3. M. H. Elnagdi, M. R. H. Elmoghayar and G. E. H. Elgemeie, *Synthesis*, 1984, 1 and the references cited therein.
4. G. E. H. Elgemeie, H. A. Elfahham, Y. R. Ibraheim and M. H. Elnagdi, *Arch. Pharm. (Weinheim)*, **322,** 535 (1989).
5. G. E. H. Elgemeie, H. A. Regaila and N. Shehata, *J. Chem. Soc. Perkin Trans. 1*, in press (1989).
6. G. E. H. Elgemeie, H. A. Elfahham and R. Mekhamer, *Sulfur Lett.*, **8,** 187 (1988).
7. G. E. H. Elgemeie, H. A. Elfahham and H. A. Nabey, *Bull. Chem. Soc. Japan*, **61,** 4431 (1988).
8. E. C. Taylor, D. C. Palmer, T. J. George, S. R. Fletcher, C. P. Tseng, P. J. Harrington and G. P. Beardsley, *J. Org. Chem.*, **48,** 4852 (1983).
9. A. I. Vogel, *A Textbook of Practical Organic Chemistry*, 4*th* Edition, Longman-England, 796 (1987).
10. J. S. A. Brunskill, Asish De, and D. F. Ewing, *J. Chem. Soc. Perkin Trans. 1*, 1978, 629.