Heteroatom Chemistry
Volume 7, Number 1, 1996

Nitriles in Heterocyclic Synthesis: A Novel Synthesis of Some Thieno[2,3-d]Pyrimidine and Thieno[2,3-b]Pyridine Derivatives

Zaghloul El-Shahat Kandeel

Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt

Received 27 April 1995; revised 7 June 1995

ABSTRACT

A simple route to the synthesis of the pharmaceutically important thieno[2,3-d]pyrimidine derivatives and of thieno[2,3-b]pyridine derivatives via the use of 5-amino-3-phenylthiophene-2,4-dicarbonitrile (2) as a starting material is described. © 1996 John Wiley & Sons, Inc.

2-Amino-3-functionally substituted thiophene derivatives are useful precursors in the azo dye industry and as intermediates for the pharmaceutically important thieno[2,3-d]pyrimidines [1,2]. In continuation of our previous work aiming at the synthesis of different heterocycles from the readily obtainable nitrile intermediates [3–7], we report here a facile and efficient route for the synthesis of some new thieno[2,3-d]pyrimidine and thieno[2,3-b]pyridine derivatives from 3-dicyanomethylene-3-phenylpropionitrile (1) [8].

When 1 was allowed to react with elemental sulfur in refluxing ethanol in the presence of a catalytic amount of piperidine, there was obtained quantitatively 5-amino-3-phenylthiophene-2,4-dicarbonitrile (2) [9].

Compound 2 reacted with trichloroacetonitrile in dry toluene in the presence of a catalytic amount of piperidine under reflux to afford the thieno-[2,3-d]pyrimidine derivative 3 in excellent yield (cf. Tables 1 and 2). Being a good leaving group [10], the trichloromethyl moiety in compound 3 permitted us to obtain in a very simple way other substituted thienopyrimidine derivatives. Thus, refluxing 3 in methanol, ethanol, or dioxane containing hydrazine readily afforded the corresponding thieno[2,3-d]pyrimidines 4a–c, respectively (Scheme 1). The structures of compounds 4a–c were deduced from their analytical and spectral data (Tables 1 and 2).

When compound 2 was heated with formic acid under reflux, a crystalline rose-colored product was formed. The mass spectrum of this product revealed a molecular ion peak *M/z* at 271 (M^+). Although the thieno[2,3-d]pyrimidine structure 6 would seem to be a reasonable possibility, the 2-formylaminothiophene-3-carboxamide structure 5 was actually assigned for this product on the basis of its IR, ^1H NMR, and ^{13}C NMR spectra (Table 2).

Attempted cyclization of 5 to the thieno[2,3-d]pyrimidine 7 by use of concd. H_2SO_4 was unsuccessful; however, this cyclization could be effected successfully by boiling 5 with acetic anhydride for a long time.

On the other hand, when compound 2 was refluxed with formamide, it afforded directly 4-amino-5-phenyl-thieno[2,3-d]pyrimidine-6-carbonitrile 8 in a high yield (Scheme 1).

Also, compound 2 was found to afford the 2-methyl-4-oxo-thieno[2,3-d]pyrimidine derivative 11 when refluxed in acetic anhydride. Formation of compound 11 presumably takes place by acetylation of the amino group in compound 2 to afford the non-isolable acetyl derivative 9 that cyclizes into 10 which then undergoes rearrangement under the reaction conditions to give 11.

When compound 2 was treated with phenyl isothiocyanate in dry acetone, it was recovered un-

1042-7163/96/010029-05

TABLE 1 Physical and Analytical Data of the New Compounds

Compound No.	Mp °C (Solvent)	Yield %	Mol. Formula (M.W)	Analysis % Found / Calcd.	C	H	N	S
3[a]	253–255 (Benzene)	54	$C_{14}H_7N_4Cl_3S$ (369.66)		45.3 45.49	2.0 1.91	15.3 15.16	8.5 8.67
4a	188–189 (Methanol)	88	$C_{14}H_{10}N_4OS$ (282.32)		59.7 59.56	3.4 3.57	20.0 19.85	11.5 11.36
4b	210 (Ethanol)	90	$C_{15}H_{12}N_4OS$ (296.35)		61.0 60.80	3.9 4.08	19.0 18.91	10.6 10.82
4c	238–240 (Dioxane)	87	$C_{13}H_{10}N_6S$ (282.32)		55.5 55.31	3.3 3.57	30.0 29.77	11.2 11.36
5	248–249 (Ethanol/DMF)	85	$C_{13}H_9N_3O_2S$ (271.29)		57.7 57.55	3.2 3.34	15.5 15.49	11.7 11.82
7	265–266 (DMF)	58	$C_{13}H_7N_3OS$ (253.28)		61.5 61.65	3.0 2.79	16.7 16.59	12.5 12.66
8	>300 (DMF)	80	$C_{13}H_8N_4S$ (252.29)		62.0 61.89	3.0 3.20	22.2 22.21	12.5 12.71
11	258–259 (Acetic acid)	62	$C_{14}H_9N_3OS$ (267.31)		63.1 62.91	3.2 3.39	15.7 15.72	12.0 11.99
13	165 (Ethanol)	56	$C_{19}H_{12}N_4S_2$ (360.45)		63.5 63.31	3.2 3.36	15.5 15.54	18.0 17.79
17a	198–200 (Ethanol)	90	$C_{21}H_{12}N_4S$ (352.41)		71.5 71.57	3.5 3.43	15.7 15.90	9.2 9.10
17b[b]	218–219 (Dioxane)	80	$C_{21}H_{11}N_4ClS$ (386.86)		65.0 65.20	3.0 2.87	14.5 14.48	8.3 8.29
17c	195–196 (Ethanol)	81	$C_{22}H_{14}N_4OS$ (382.44)		68.9 69.09	3.8 3.69	14.5 14.65	8.5 8.38
17d	214 (Ethanol)	82	$C_{19}H_{10}N_4OS$ (342.38)		66.6 66.65	3.0 2.94	16.5 16.37	9.5 9.36
17e	223 (Ethanol)	79	$C_{19}H_{10}N_4S_2$ (358.44)		63.5 63.67	3.0 2.81	15.7 15.63	18.0 17.89

[a]Cl; found 29.0, calcd. 28.77%.
[b]Cl; found 9.1, calcd. 9.16%.

changed; however, when the reaction was carried out in dioxane in the presence of a catalytic amount of triethylamine, a crystalline product was obtained. The thieno[2,3-d]pyrimidine structure **13** was assigned to this product on the basis of elemental analysis and spectral data (Table 2).

Formation of compound **13** is assumed to take place via the nonisolable intermediate **12** that cyclizes into **13** under the reaction conditions (Scheme 2). Similarly, compound **2** reacted with the arylidene malononitrile derivatives **14** to afford the thieno[2,3-b]pyridine derivatives **17a–d** in good yields. The structures of compounds **17a–d** were confirmed on the basis of their elemental analyses and spectral data (Table 2).

Formation of compounds **17a–d** is assumed to take place via the initial Michael addition of the amino group in compound **2** to the activated double bond in **14** to give the nonisolable intermediate **15** that cyclizes into **16**, which then loses hydrogen cyanide to afford the thieno[2,3-b]pyridines **17a–d** (Scheme 2).

EXPERIMENTAL

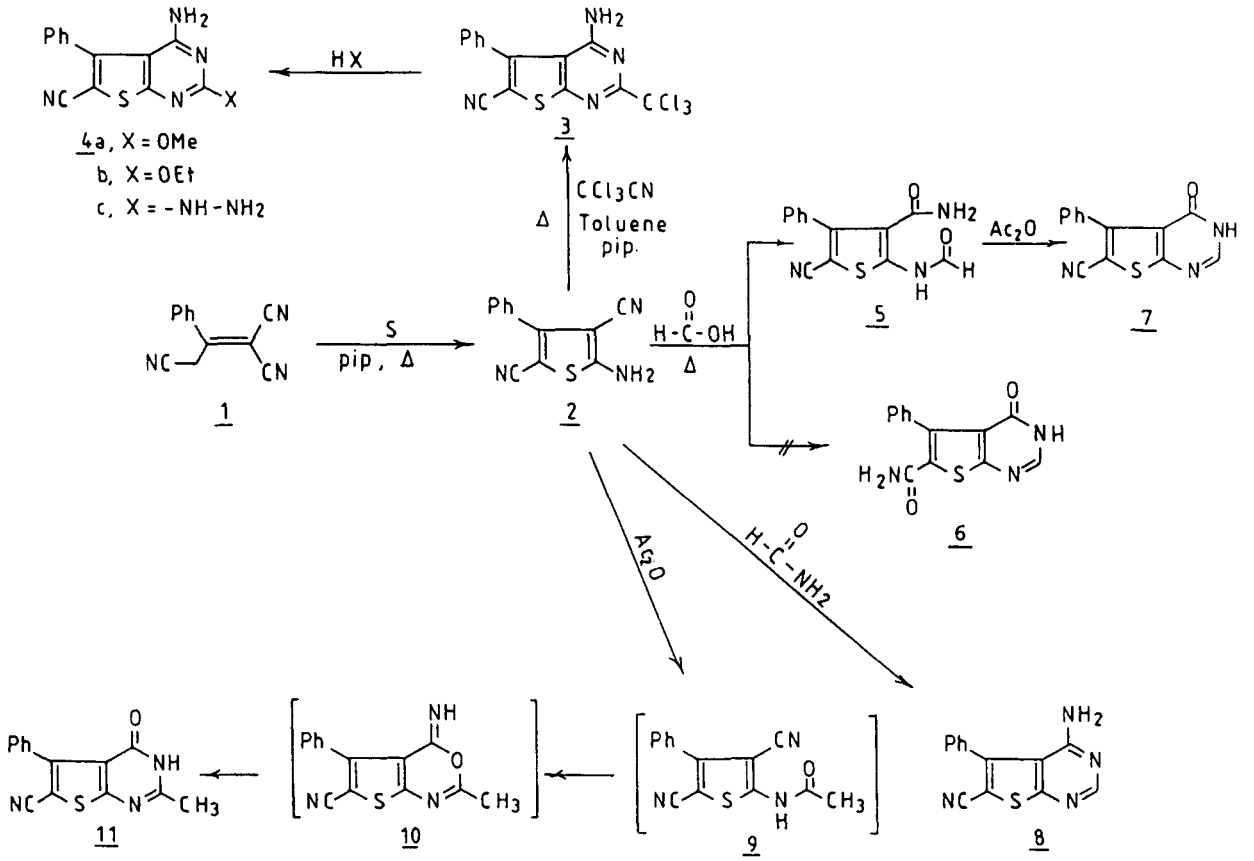
Melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. The IR spectra were taken as KBr discs on a Perkin-Elmer FT IR 1650 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer for solutions in $CDCl_3$ or DMSO-d_6, with TMS as an internal standard. Mass spectra were obtained on a GCMS-QP 1000 Ex mass spectrometer with an ionization potential of 70 eV. Microanalyses were performed at the Microanalytical Center at Cairo University.

5-Amino-3-phenylthiophene-2,4-dicarbonitrile (2)

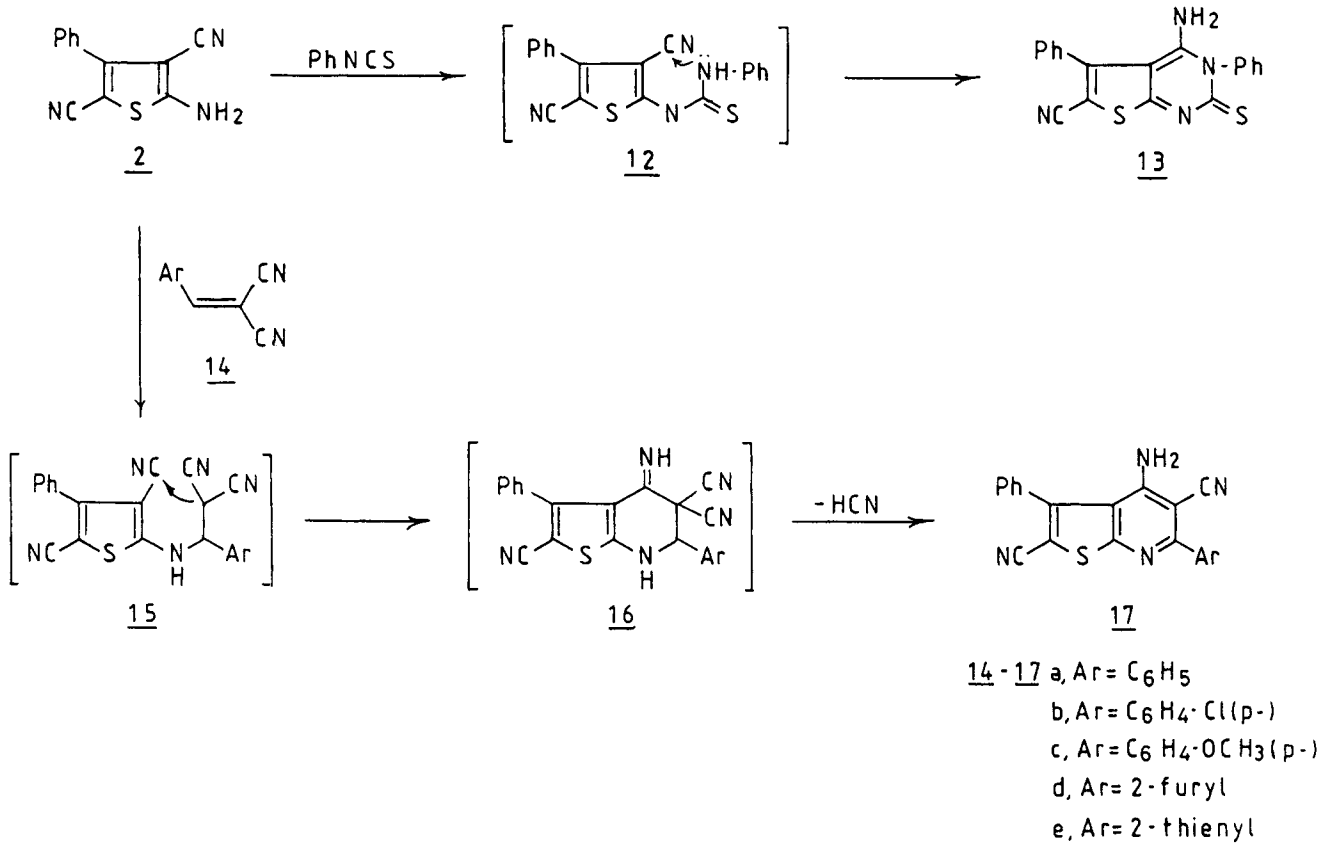
To a solution of 19.3 g (0.1 mol) of 1,1,3-tricyano-2-phenylpropene (**1**) in ethanol (100 mL) was added 3.52 g (0.11 mol) of elemental sulfur and a catalytic amount of piperidine. The reaction mixture was heated under reflux for 5 hours, then allowed to cool to room temperature. The precipitated grayish yel-

TABLE 2 Spectral Data of the Prepared Compounds

Compound No.	*IR (ν, cm⁻¹),*	*¹H NMR, δ*	*MS*
3	3160–3100(NH_2), 2214(CN), 1670(C=N)	4.62(s, 2H, NH_2), 7.82–8.15(m, 5H, arom. H)	
4a	3150–3080(NH_2), 2974(–CH_3), 2216(CN)	3.72(s, 3H, CH_3), 4.63(s, 2H, NH_2), 7.62–7.95(m, 5H, arom. H)	
4b	3160–3090(NH_2), 2940(aliphatic CH), 2217(CN)	1.05(t, 3H, CH3), 3.44(q, 2H, CH_2), 4.5(s, 2H, NH_2), 7.82–8.17(m, 5H, arom. H)	
4c	3500–3200(br., NH, NH_2), 2216(CN)	3.35(s, 2H, NH_2), 4.53(s, 2H, NH_2), 5.42(s, 1H, NH), 7.83–7.95(m, 5H, arom. H)	
5	3465, 3342(NH_2), 3151(NH), 2213(CN), 1658(C=O)	5.35(s, 2H, NH_2), 7.40–7.85(m, 5H, arom. H), 8.70(s, 1H, NH), 12.5(s, 1H, CH)	271
7	3266, 3228(NH), 2217(CN), 1700(C=O), 1555(C=C)	7.35–7.80(m, H, arom. H), 8.7(s, 1H, pyrim-2-H), 9.82(s, 1H, NH)	253
8	3448, 3295(NH_2), 2218(CN), 1640(C=N)	5.20(s, 2H, NH_2), 7.32–7.85(m, 5H, arom. H), 9.75(s; 1H, NH)	252
11	3264(NH), 3055(CH_3), 2216(CN), 1699(C=O), 1555(C=N)	2.26(s, 3H, CH_3), 7.50–7.81(m, 5H, arom. H), 8.88(s, 1H, NH)	
13	3400, 3300(NH_2), 2220(CN), 1658(C=S)	4.28(s, 2H, NH_2), 7.52–7.83(m, 10H, arom. H)	360
17a	3450, 3360(NH_2), 2220, 2216(CN)	5.22(s, 2H, NH_2), 7.38–7.82(m, 10H, arom. H)	352
17b	3446, 3340(NH_2), 2222, 2218(two CN)	5.17(s, 2H, NH_2), 7.50–7.82(m, 9H, arom. H)	
17c	3460, 3290(NH_2), 2221, 2217(CN)	3.72(s, 3H,–CH_3), 4.98(s, 2H, NH_2), 7.60–8.00(m, 9H, arom. H)	
17d	3450, 3320(NH_2), 2221, 2216(two CN)	4.92(s, 2H, NH_2), 7.32–7.79(m, 8H, arom. H)	
17e	3462, 3310(NH_2), 2222, 2218(two CN)	5.00(s, 2H, NH_2), 7.34–7.78(m, 8H, arom. H)	



SCHEME 1



SCHEME 2

low solid was filtered off and recrystallized from ethanol to give 21.2 g (94%) of 2. M.p. 243–244°C lit. [9] M.p. 244–245°C.

4-Amino-2-trichloromethyl-5-phenylthieno[2,3-d]pyrimidine-6-carbonitrile (3)

To a suspension of 2.25 g of **2** (0.01 mol) in dry toluene (20 mL) was added 1 mL (0.01 mol) of trichloroacetonitrile followed by 3 drops of piperidine as a catalyst. The reaction mixture was heated under reflux for 3 hours, then left to cool. The precipitated crystalline brownish solid obtained was filtered off, washed with petroleum ether (20 mL), and recrystallized from benzene to afford 2.0 g of **3**.

4-Amino-5-phenyl-2-substituted Thieno[2,3-d]pyrimidine-6-carbo-nitriles **4a–c**

Compound **3** (0.37 g, 0.001 mol) was refluxed in absolute methanol (10 mL), ethanol (10 mL) for 2 hours, or in 20 mL of dioxane containing an excess (1 mL) of hydrazine hydrate for 3 hours. The solution obtained in each case was filtered while hot for recrystallization. The solids that precipitated after cooling or dilution with cold water were filtered off to give 0.25 g of **4a**, 0.27 g of **4b**, and 0.25 g of **4c**, respectively.

5-Cyano-2-formylamino-4-phenylthiophene-3-carboxamide (5)

The dicarbonitrile **2** (2.25 g, 0.01 mol) was added to 15 mL of formic acid and the mixture was heated under reflux for 3 hours. The excess formic acid was evaporated under reduced pressure, and the remainder was poured on crushed ice (50 g) and neutralized with NH_4OH solution. The precipitated rose-colored solid was collected by filtration, washed with water, and recrystallized from ethanol-DMF to give 2.31 g of **5** as rose-colored needles. ^{13}C NMR ($CDCl_3$): 96.51, 107.87, 129.27, 129.69, 129.78, 130.40, 132.31, and 158.33.

3-Phenyl-4-oxo-thieno[2,3-d]pyrimidine-2-carbonitrile (7)

A solution of 1 g of compound **5** in acetic anhydride (10 mL) was heated under reflux for 6 hours. The solvent was removed by evaporation under reduced

pressure and the remainder was poured into water (15 mL). The solid product thus formed was collected by filtration, washed with water, and recrystallized from DMF to provide 0.55 g of compound **7**.

4-Amino-5-phenylthieno[2,3-d]pyrimidine-6-carbonitrile (**8**)

A solution of **2** (2.25 g, 0.01 mol) in 25 mL of formamide was heated under reflux for 2 hours, at which time the color darkened. After having been cooled to room temperature, the precipitated solid was collected by filtration, washed with ethanol, and recrystallized from DMF to provide 2.02 g of **8**.

2-Methyl-4-oxo-5-phenylthieno[2,3-d]pyrimidine-6-carbonitrile (**11**)

Compound **2** (2.25 g, 0.01 mol) was added to 20 mL of acetic anhydride. The reaction mixture was heated under reflux for 4 hours. The solvent was removed by evaporation under reduced pressure, and the remainder was poured into ice water. The crystalline solid formed was collected by filtration, washed with water, and recrystallized from acetic acid (Table 1).

4-Amino-1,3-diphenyl-2-thiocarbonylthieno[2,3-d]pyrimidine-6-carbonitrile (**13**)

To a solution of **2** (2.25 g, 0.01 mol) in dioxane (20 mL) was added phenyl isothiocyanate (1.35 g, 0.01 mol) and 2–3 drops of triethylamine as a catalyst, and the reaction mixture was heated under reflux for 6 hours and then allowed to cool to room temperature. The crystalline brownish solid that had formed was collected by filtration, washed with water, dried, and recrystallized from ethanol to provide 2.02 g of **13**.

4-Amino-2,5-diarylthieno[2,3-d]pyridine-3,6-dicarbonitriles **17a–d**

General Procedure. To a solution of 2.25 g (0.01 mol) of **2** in ethanol (30 mL) was added 0.01 mole of each of the arylidene malononitriles **14a–d** and 2–3 drops of piperidine as a catalyst. Each reaction mixture was heated under reflux for 6 hours. The solvent was removed by evaporation under reduced pressure, and the remainder was poured into ice water. The solid materials formed in each case were collected by filtration, washed with water, dried, and recrystallized from ethanol to afford 3.17 g of **17a**, 3.21 g of **17b**, 3.10 g of **17c**, and 2.83 g of **17d**, respectively.

ACKNOWLEDGMENT

The author thanks Prof. Dr. T. Fuchigami, Tokyo Institute of Technology, for taking ^{13}C and ^{1}H NMR spectra of some samples cited in this article.

REFERENCES

[1] D. L. Temple, J. P. Yevich, R. R. Convington, C. A. Hanning, R. J. Seidehamel, H. K. Mackey, M. J. Bartek, *J. Med. Chem., 22,* 1979, 505.
[2] A. Jotterand: German Patent no. 2,359,008,06 (June 1974), C.A. *81,* 137599.
[3] T. Fuchigami, Z. E. Kandeel, T. Nonaka, *Bull. Chem. Soc. Jpn., 58,* 1985, 2441.
[4] E. A. A. Hafez, Z. E. Kandeel, M. H. Elnagdi, *J. Heterocyclic Chem., 24,* 1987, 227.
[5] Z. E. Kandeel, K. M. Hassan, N. A. Ismail, M. H. Elnagdi, *J. Prakt. Chem., 326,* 1984, 248.
[6] Z. E. Kandeel, F. M. Abdelrazek, N. E. M. Salah Eldin, M. H. Elnagdi, *J. Chem. Soc. Perkin Trans., I,* 1985, 1499.
[7] Z. E. Kandeel, T. Fuchigami, T. Nonaka, *J. Chem. Soc. Perkin Trans, I,* 1986, 1379.
[8] Z. E. Kandeel, A. M. Farag, F. M. Abdelrazek, *Heteroatom Chem., 6,* 1995, 281.
[9] D. Reux, F. Pochat, *Sulfur Lett., 13,* 1991, 197.
[10] F. M. Abdelrazek, *Z. Naturforsch., 44b,* 1989, 488.