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Heterocyclic Synthesis with Nitriles: A New Approach to Thiophene and Thieno-[2,3-d]-pyrimidine Derivatives

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Abstract α-Cyano-β-thiocyanatomethyl cinnamonitrile (**1**) was transformed into 5-acetyl-2-amino-4-phenylthiophen-3-carbonitrile (**3**) on refluxing in acetic/sulphuric acid mixture. Compound **3** reacted with trichloroacetonitrile, formamide, carbon disulphide and ethylorthoformate.

In continuation with our previous work aiming to develop new simple procedures for synthesis of azoles, azines and their condensed derivatives [1–4], utilizing the readily obtainable polyfunctional nitriles, we report a new synthesis of substitued thiophene and thieno-[2,3-d]-pyrimidine derivatives from α-cyano-β-thiocyanatomethyl cinnamonitrile (**1**) [5].

Thus, when compound **1** was refluxed in acetic/sulphuric acid mixture for 2 hrs, a greenish product was obtained. Elemental analysis of this product showed that it contains sulpher i. r. spectrum of this product, however, showed only one cyano absorption band at ν 2180 cm^{-1} together with a carbonyl absorption band at ν 1660 cm^{-1}. ^{1}H-n.m.r. spectrum showed a singlet (3H) at δ 2.5 ppm assignable to CH_3, a singlet (2H) at δ 7.3 ppm for NH_2 together with aromatic multiplet at δ 7.35–7.85 ppm. The presence of carbonyl absorption in the i. r. and CH_3 in the ^{1}H-n.m.r. spectra has made some confusion in constructing the structure of the product, especially when more than one structure can has nearly the same analytical data. Mass spectroscopy has afforded a conclusive evidence of structure **3**, which was established for this reaction product. Thus, it showed that M + 1 at 243, a peak at 43 (CH_3CO) and another at 77 (phenyl group).

The formation of **3** from **1** can be assumed to proceed via initial hydrolysis of the thiocyanate group into-SH followed by intramolecular addition to the neighbouring CN group to afford compound **2**, which was not separated and underwent, in the same reaction flask, acetylation in the free 5 position to afford compound **3** (scheme 1). This assumption finds parallelism with the reported literature[6].

β-Enaminonitriles have been extensively utilized in heterocyclic synthesis [5, 7, 8]. The enaminonitrile moiety in compound **3** has been explored for further chemical transformations. Thus compound **3** reacted with trichloroacetonitrile in refluxing ethanol to afford a product, for which structure **4** was assigned on the basis of analytical and spectral data. The trichloromethyl moiety being substituted by ethoxy group upon reflux in ethanol [5]. Our trials to cyclize **4** into the thienopyrimidine **5** were unsuccessful. Analytical and ^{1}H-n.m.r. data are of no help in discriminating structures **4** and **5**, however, the presence of cyano absorption band at ν 2190 cm^{-1} in the i.r. chart of the product gives a conclusive evidence of structure **4**.

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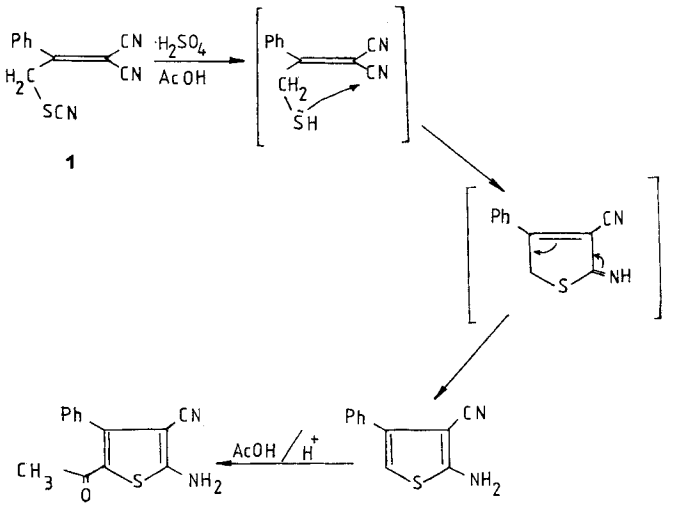
Compound **3** reacted also with carbon disulphide in pyridine to afford the thienopyrimidine dithione **6** [9].

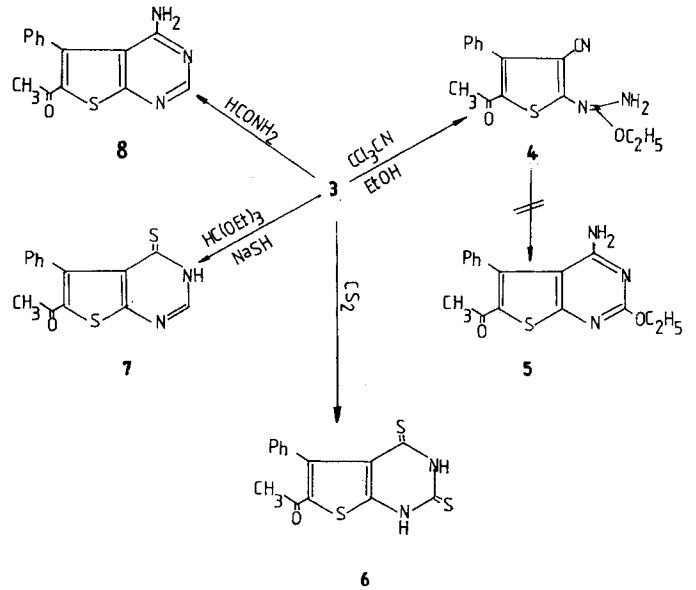


1 **3** **2**

When compound **3** was reacted with ethylorthoformate followed by sodium hydrogen sulphide according to TAYLOR et al. [10], a yellowish product was obtained for which the thienopyrimidine thione structure **7** was assigned on the basis of analytical and spectral data.

Compound **3** undergoes cyclocondensation when refluxed in formamide [11] to afford the thienopyrimidine **8**.

The obtained thienopyrimidines and thienopyrimidinethiones seem to be interesting for biological and pharmaceutical studies [12].



8 **4** **7** **5** **6**

Table 1 Analytical and spectral data of newly prepared compounds **3**, **4**, **6**, **7**, **8**

Compd. No.	Yield %	m.p. °C (solvent)	Mol. Formula (Mol. Wt.)	Analysis: Calcd/Found C	H	N	S	i.r. ν (cm^{-1}) (select. bands)	^{1}H-n.m.r. (δ ppm)
3	70	212 (AcOH)	$C_{13}H_{10}N_2OS$ (242.3)	64.44 64.14	4.16 4.10	11.56 11.53	13.23 13.14	3400–3200 ($NH)_2$, 2180(CN),1660 (CO)	2.5 (s, 3H, CH_3), 7.3–7.85 (m, 7H C_6H_5 and NH_2).
4	40	85 (EtOH)	$C_{16}H_{15}N_3O_2S$ (313.4)	61.32 61.03	4.82 4.72	13.41 13.39	10.23 10.08	3380–3250 (NH_2), 2190 (CN), 1680 (CO)	1.85 (t, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.7 (q, 2H, CH_2), 5.8 (s, 2H, NH_2), 7.3–7.7 (m, 5H, C_6H_5).
6	78	185 (DMF)	$C_{14}H_9N_2OS_3$ (317.4)	52.98 52.58	2.86 2.51	8.83 8.43	30.31 29.87	3400–3190 (br. NH), 1675 (CO)	2.63 (s, 3H, CH_3), 7.3–8.0 (m, 5H, C_6H_5), 9.8 (s, 1H, NH).
7	67	230 (DMF)	$C_{14}H_{10}N_2OS_2$ (286.4)	58.71 58.39	3.52 3.32	— —	22.39 22.14	3380–3200 (br. NH), 1680 (CO).	
8	45	98 (DMF)	$C_{14}H_{11}N_3OS$ (269.3)	62.44 62.27	4.12 4.00	— —	11.91 11.46	3240–3250 (NH_2), 1675 (CO).	2.55 (s, 3H, CH_3), 7.27–7.9 (m, 7H, C_6H_5 + NH_2), 8.6 (s, 1H, pyrimidine C^2H).

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Experimental

All melting points are uncorrected. I.r. spectra were recorded as KBr discs using a Pye-Unicam SP-1100 spectrophotometer. ^{1}H-n.m.r. spectra were recorded on a Varian A-60 spectrometer using TMS as internal standard. Chemical shifts are expressed as ppm. Analytical data were obtained from the microanalytical centre at Cairo University. Mass spectra were taken on Varian Mat 111 and Vac. generators 70—70.

5-Acetyl-2-amino-4-phenylthiophen-3-carbonitrile (**3**)

To a solution of 2.25 gm (0.01 mole) of **1** in 25 ml glacial acetic acid was added 2 ml conc. sulphuric acid and 1 ml water. The reaction mixture was refluxed for 2 hrs, left to cool at room temperature. The greenish precipitated solid so formed was then filtered and recrystallized from acetic acid to afford 1.7 gm of **3**.

5-Acetyl-2-ethoxyformamidino-4-phenylthiophen-3-carbonitrile (**4**)

To a solution of **3** (2.42 gm, 0.01 mole) in 25 ml absolute ethanol was added trichloroacetonitrile (1.45 gm, 0.01 mole) and a catalytic amount of piperidine. The reaction mixture was refluxed on a water bath for 2 hrs, at which time the colour darkens, then left to cool and filtered off. The solid product so formed was recrystallized to afford 1.25 gm of compound **4**.

6-Acetyl-5-phenyl-2,4-dithoxo-1,2,3,4-tetrahydrothieno[2,3-d] pyrimidine (**6**):

A solution of **3** (2.42 gm, 0,01 mole) in a mixture af 10 ml dry pyridine and 10 ml carbon disulphide was refluxed on a water bath for 3 hrs, then allowed to stand for 3 days at room temperature. The solution was then diluted with ethanol (100 ml). The precipitated solid was filtered off, washed with ethanol and recrystallized from DMF to afford 2.5 gm of the dithione **6**.

6-Acetyl-5-phenyl-4-thioxo-3,4-dihydrothieno[2,3-d] pyrimidine (**7**).

A solution of **3** (2.42 gm, 0.01 mole) in a mixture of 20 ml ethylorthoformate and 20 ml acetic anhydride was refluxed for 2 hrs. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was dissolved in about 50 ml 1.5 N sodium hydrogen sulphide in absolute ethanol. The resulting solution was refluxed for 7 hrs and left to cool overnight in open atmosphere. The residue was treated with water, boiled with charcoal and filtered. On acidification with glacial acetic acid, a yellowish product separated, filtered and recrystallized from DMF to afford 1.9 gm of **7**.

6-Acetyl-4-amino-5-phenylthieno [2,3-d] pyrimidine (8)

A solution of compound **3** (1.21 gm, 0.005 mole) in formamide (20 ml) was refluxed for 2 hrs at which time the colour turns to dark green. After cooling, the precipitated solid is collected by filteration and recrystallized to give 0.6 gm of **8**.

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