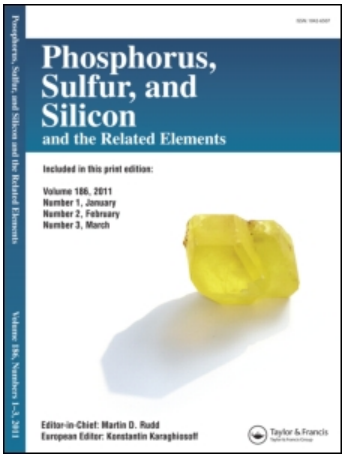

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HETEROCYCLIC SYNTHESIS WITH NITRILES: SYNTHESIS OF SOME NEW THIOPHENE AND THIENO[2,3-*d*]PYRIMIDINE DERIVATIVES IV[1]

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α-(thiocyanatomethyl) benzylidenemalononitrile (**1**) undergoes hydrolysis followed by cyclization to afford 2-amino-4-phenylthiophene-3-carbonitrile (**2**) on reflux in acetic/dil. hydrochloric acid mixture. Compound **2** reacts with dil. sulfuric acid, phenacyl bromide, potassium hydroxide, and phenyl isothiocyanate to afford the thiophene derivatives **3**, **8**, **15** and **17** respectively. The reaction of **2** with acetic anhydride, benzoylacetonitrile, phenacyl thiocyanate, and benzoyl isothiocyanate led to the formation of the thieno[2,3-*d*] primidine derivatives **7**, **10**, **11**, **13** and **18** respectively.

Keywords: α-(thiocyanatomethyl)benzylidenemalononitrile; thiophene derivatives; thieno[2;3-*d*]pyrimidine derivatives

2-Amino-3-functionally substituted thiophenes are still attracting attention as useful intermediates to the pharmaceutically important thieno[2,3-*d*]pyrimidine derivatives.[2–4] We previously reported[5] that α-(thiocyanatomethyl) benzylidenemalononitrile (**1**) underwent cyclization under different reaction conditions to afford substituted 2-aminothiophenes. In the context with our previous work[1,5–8] to synthesize new functionally substituted heterocylcic systems of anticipated biological activity, the synthesis of some new thiophene and thieno[2,3-*d*]pyrimidine derivatives is now reported. These compounds were required for testing as potential biodegradable agrochemicals.

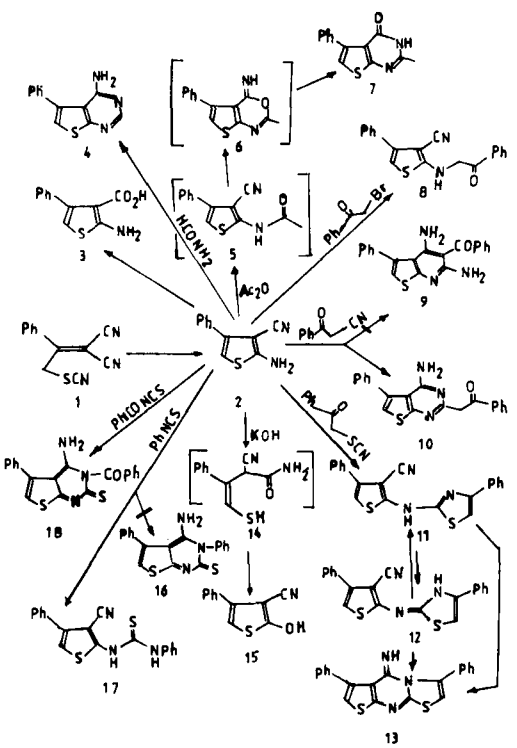
Refluxing compound **1** in a acetic/dil. hydrochloric acid mixture for two hours afforded a greenish product with mp 174°C. The IR spectrum of this product showed a broad absorption band at ν 3380-3150 cm^{-1} and a sharp cyano absorption band at ν 2185 cm^{-1}. The ^{1}H-NMR spectrum of this product revealed a singlet (1 H) at δ 6.8 besides an aromatic multiplet (7 H) at 7.2–7.9 ppm. The

elemental analyses were found to be consistent with a molecular formula $C_{11}H_8N_2S$. On these bases the thiophene structure **2** was assigned to this product.

The structure of compound **2** was unambiguously confirmed when it afforded 2-amino-4-phenylthiophene-3-carboxylic acid (**3**) upon reflux in a dil. sulfuric acid solution. Compound **3** has been previously described by us.[5] The identity of the two products was based on mp and TLC analysis.

Compound **2** underwent cyclocondensation when refluxed in formamide to afford the thienopyrimidine derivative **4**.[6] Analytical and spectral data are consistent with structure **4** (Scheme 1, Tables I and II).

Compound **2** reacted with acetic anhydride to yield the 2-methyl-4-oxothieno[2,3-*d*]pyrimidine derivative **7** presumably via *N*-acetylation to afford **5** which apparently cyclized into **6** which then in turn rearranged to **7** (Scheme 1). A similar behavior has been previously reported.[7]



SCHEME 1

TABLE I Physical and analytical data of the newly prepared compounds

Compd. No.	MP °C Solvent	Yield %	MF MW	Calcd. found C	Analysis % H	N
2	174	88	$C_{11}H_8N_2S$	65.97	4.03	13.99
	EtOH		200.26	65.63	4.04	14.14
4	86	66	$C_{12}H_9N_3S$	63.41	3.99	18.49
	EtOH		227.29	63.08	4.24	18.69
7	253	78	$C_{13}H_{10}N_2OS$	64.44	4.16	11.56
	DMF		242.30	64.60	4.34	11.33
8	241	75	$C_{19}H_{14}N_2OS$	71.67	4.43	8.80
	AcOH		318.40	71.72	4.54	8.58
10	293	65	$C_{20}H_{15}N_3OS$	69.54	4.38	12.16
	DMF		345.42	69.73	4.63	12.14
11	157	67	$C_{20}H_{13}N_3S_2$	66.83	3.64	11.69
	EtOH		359.47	67.04	3.86	12.01
13	286	89	$C_{20}H_{13}N_3S_2$	66.83	3.64	11.69
	DMF		359.47	67.05	3.51	11.74
15	144	82	$C_{11}H_7NOS$	65.65	3.51	6.96
	EtOH		201.25	65.54	3.72	7.08
17	218	55	$C_{18}H_{13}N_3S_2$	64.45	3.91	12.53
	DMF		335.45	64.64	4.17	12.82
18	305	53	$C_{19}H_{13}N_3OS_2$	62.79	3.60	11.56
	DMF		363.46	62.94	3.42	11.82

Similarly the reaction of **2** with phenacyl bromide led to *N*-alkylation. In this case the *N*-phenacyl derivative **8** was not further cyclized under the reaction conditions.

Benzolyacetonitrile reacted with **2** to afford a 1 : 1 adduct for which structures **9** or **10** can be considered. The presence of a methylene singlet at $\delta \sim 3.4$ in the ^{1}H-NMR spectrum of this adduct suggested structure **10** over **9**. The IR spectrum and elemental analysis were in complete agreement with structure **10**.

Compound **2** reacted also with phenacyl thiocyanate in refluxing ethanol catalyzed by HCl to afford a 1 : 1 adduct. The IR spectrum of this product showed absorption bands at ν 3400-2900 and 2195 cm^{-1} assignable to NH and CN groups respectively. The ^{1}H-NMR spectrum revealed two singlets at δ 6.6 and δ 6.8, an aromatic multiplet (10 H) at δ 7.3–8.1, and an NH singlet at δ 11.8. The *N*-(thiazol-2-yl) derivative **11**, or its tautomeric structure **12**, was assigned to this product. It seems, however, that structure **11** predominated under acidic and neutral conditions, otherwise, if structure **12** was the predominant isomer, cyclization to **13** would have been expected. In support of this assumption, our product was cyclized into **13** upon reflux in ethanol catalyzed by triethylamine. The cyclization was inferred from the disappearance of the cyano absorption

TABLE II Spectral data of the newly prepared compounds

Compd. No.	*IR ν cm^{-1} Selected bands*	*^{1}H-NMR δ*
2	3380 – 3150 (NH_2), 2185(CN)	6.8 (S, 1 H, Thiophene 5-H), 7.2–7.9 (m, 7 H, Ar. + NH_2).
4	3320 – 3240 (NH_2).	6.83 (s, 1 H, thiphene 5H), 7.25–7.9 (m, 7 H, Ar. + NH_2), 8.65 (s, 1 H, pyrimidine H).
7	3180(br.NH), 1650 (CO).	2.2 (s, 3 H, CH_3), 6.8 (s, 1 H), 7.3–7.95 (m, 5 H, Ar.H), 8.7 (s, 1 H, NH).
8	3250 (br.NH), 2188 (CN), 1680 (CO).	3.35 (s, 2 H, CH_2), 6.8 (s, 1 H), 6.95 (s, 1 H, NH), 7.25–7.95 (m, 10 H, Ar. H).
10	3270 (br.NH_2), 1670 (CO).	3.38 (s, 2 H, CH2), 6.82 (s, 1 H), 7.35–7.95 (m, 10 H, Ar.H), 8.1 (s, 2 H, NH_2).
11	3400 – 2900 (br.NH), 2195 (CN).	6.6 (s, 1 H, thiazole 5-H), 6.8 (s, 1 H, thiophene 5-H), 7.3–8.1 (m, 10 H, Ar. H), 11.8 (s, 1 H, NH).
13	3210 (br.NH).	6.62 (s, 1 H), 6.85 (s, 1 H), 7.3–7.95 (m, 10 H, Ar. H), 11.2 (s, 1 H, NH).
15	3450 (OH), 2187 (CN).	6.82 (s, 1 H), 6.95 (s, 1 H, OH), 7.2–7.9 (m, 5 H, Ar. H).
17	3400 – 3250 (NH), 2178 (CN).	6.55 (s, 1 H, NH), 6.81 (s, 1 H), 7.3–8.2 (m, 11 H, Ar. H + NH).
18	3410 – 3370 (NH_2), 1678 (CO).	6.81 (s, 1 H), 7.2–8.1 (m, 12 H, Ar. H + NH_2).

band in the IR spectrum of **13**. A similar reaction has been reported,[9] however, the angular isomer is excluded in our case since **13** was obtained from the cyclization of **11** and was not a direct product of the reaction.

Compound **2** underwent hydrolytic ring opening and recyclization upon reflux in 10% KOH solution to afford a new product different from **2** in both color and mp. Different structures can be considered for this product arising from the hydrolysis intermediate **14** by elimination of H_2S, H_2O, or NH_3. Element test and elemental analysis showed the presence of sulfur and suggested that ammonia was eliminated. Structure **15** was therefore assigned for this product (see Tables I and II). A similar result has been reported.[10]

Compound **2** reacted also with phenyl isothiocyanate to afford a product the IR spectrum of which showed a cyano absorption band at ν 2178 cm^{-1}. The thienopyrimidine structure **16** was therefore excluded and the thiourea derivative**17** was assigned for this product. Contrary to this, the reaction of **2** with

benzoyl isothiocyanate led to the cyclized product **18**. The IR spectrum of **18** did not show any absorption bands that can be attributed to the presence of a cyano group.

This result parallells our previous observation about these two reagents.[1] The cyclization in the second case may be enhanced by the presence of the carbonyl group and may be inhibited in the first case due to stereochemical aspects.

Experimental

All melting points were uncorrected and were taken on a Gallenkamp melting point apparatus. IR spectra were recorded in KBr pellets on a Pye-Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were taken on a Varian EM-390 (90 MHz) spectrometer in DMSO-d_6 using TMS as internal standard and expressed in δ. Microanalyses were performed by the Microanalytical Center of Cairo University.

2-Amino-4-phenylthiophene-3-carbonitrile (2)

To a solution of 2.25 g (0.01 mole) of **1** in 25 ml of acetic acid was added 5 ml of 5 *N* hydrochloric acid. The reaction mixture was refluxed for 2 h, then left to cool to room temperature, poured into ice-cold water, and neutralized with ammonia. The precipitated solid was filtered off and recrystallized from acetic acid to afford 1.75 g (88%) of **2**.

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

A solution of compound **2** (2 g; 0.01 mole) in 20 ml of formamide was refluxed for 2 h at which time the colour darkened. After cooling overnight, the precipitated solid was collected by filtration and recrystallized to give 1.5 g (66%) of **4**.

2-Methyl-5-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidne-4-one (7)

A solution of **2** (2 g; 0.01 mole) in 20 ml of acetic anhydride was refluxed for 3 h and then left to cool overnight. The solid product that appeared was filtered off and recrystallized to give 1.9 g (78%) of **7**.

2-(*N*-phenacyl)amino-4-phenylthiophene-3-carbonitrile (8)

To a solution of **2** (2 g; 0.01 mole) in 20 ml of ethanol was added phenacyl bromide (1.99 g; 0.01 mole) and K_2CO_3 (1.38 g; 0.01 mole, dissolved in the

least amount of water). The reaction mixture was refluxed for 2 h and then left overnight. The solid product was filtered off and recrystallized to afford 2.4 g (75%) of **8**.

4-Amino-2-phenacyl-5-phenylthieno[2,3-*d*]pyrimidine (10)

To a solution of **2** (2 g; 0.01 mole) in 20 ml of DMF was added 1.45 g (0.01 mole) of benzoylacetonitrile followed by 0.5 ml of piperidine. The reaction mixture was refluxed for 2 h and then left to cool. The precipitated solid was collected and recystallized from the proper solvent (Table I) to afford 2.25 g (65%) of **10**.

2-*N*-(4-phenylthiazol-2-yl)amino-4-phenylthiophene-3-carbonitrile (11)

A mixture of **2** (2 g; 0.01 mole) and phenacyl thiocyanate (1.77 g; 0.01 mole) was dissolved in 20 ml of ethanol. To this solution was added 2 ml of conc HCl, and the reaction mixture was heated on a boiling water bath for 7 h and then left to cool overnight. The precipitated solid product was filtered off and recrystallized to yield 2.4 g (67%) of **11**.

3,5-Diphenyl-4-iminothiazolo[3,2-*a*]thieno[2,3-*d*]pyrimidine (13)

To a solution of **11** (1.8 g; 0.005 mole) in 20 ml of ethanol was added 0.5 ml of triethylamine as catalyst. The mixture was refluxed for 1 h and then cooled to room temperature. The solid product was collected and recrystallized to afford 1.6 g (89%) of **13**.

2-Hydroxy-4-phenylthiophene-3-carbonitrile (15)

In 15 ml of 10% KOH solution was suspended 2 g (0.01 mole) of **2**. The emulsion was refluxed for 1 h whereupon it became clear and a precipitate reappeared during the reflux. The reaction mixture was allowed to cool to room temperature, poured on cold water and neutralized with HCl, the solid precipitate was collected by filtration and recrystallized to give 1.65 g (82%) of **15**.

N-Phenyl-N'-(3-cyano-4-phenylthien-2-yl)thiourea (17)

To a solution of **2** (2 g; 0.01 mole) in dry acetone (20 ml) was added phenyl isothiocyanate (1.35 g; 0.01 mole), and the reaction mixture was refluxed for 2

h. The precipitated solid obtained on cooling was filtered off and recrystalized to afford 1.85 g (55%) of **17**.

4-Amino-3-benzoyl-5-phenyl-2,3-dihydrothieno[2,3-*d*]-pyrimidine-2-thione (18)

To 0.01 mole of benzoyl isothiocyanate (prepared *in situ* from benzoyl chloride and ammonium thiocyanate) in dry acetone was added **2** (2 g; 0.01 mole), and the reaction mixture was refluxed for 2 h. On cooling, a solid product was separated, filtered off, and recrystalized to afford 1.9 g (53%) of **18**.

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