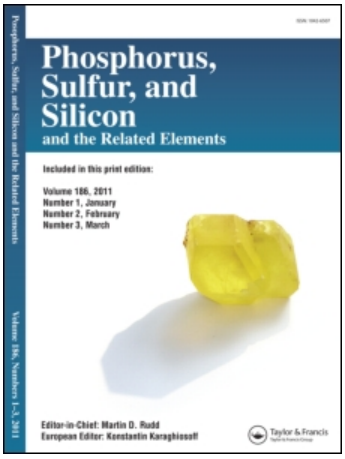

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HETEROCYCLIC SYNTHESIS WITH NITRILES: SYNTHESIS OF SOME NOVEL THIOPHENE AND THIENO[2,3-d]PYRIMIDINE DERIVATIVES

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Dedicated to Prof. M. H. Elnagdi on the occasion of his 50th birthday

The thiophene derivative **1** reacts with acrylic acid derivatives **2a-c** to give *N*-alkylated derivatives **3a–c** which all undergo further hydrolysis to afford *N*-(thien-2-yl)-β-alanine derivative **6**. While **1** reacts with phenyl isothiocyanate to afford the thiourea derivative **8**, it reacts with benzoyl isothiocyanate to afford the dihydrothieno [2,3-*d*]pyrimidine derivative **9**. Compound **1** reacts also with diethyl malonate, thiourea **14a** and guanidine **14b** to afford the thieno[2,3-*d*] pyrimidine derivatives **13**, **15a** and **15b** respectively. Benzaldehyde condenses with **1** to give the benzylidene derivative 17 which cyclizes with thioglycollic acid to afford **18**.

Key words: 5-acetyl-2-amino-4-phenylthiophene-3-carbonitrile; β-alanine derivative; thieno[2,3-*d*]-pyrimidine derivatives; N-substituted 2-phenylthiazolidin-4-one derivative.

The increasing importance of thiophene and its derivatives as intermediates to biologically active compounds and in organic synthesis has led to continuing development of new simple procedures for their synthesis.[1–3] In context with our program aiming to develop new simple routes to potential biodegradable agrochemicals from laboratory available starting materials,[4–6] we have recently reported a novel synthesis of 5-acetyl-2-amino-4-phenylthiophene-3-carbonitrile **1**,[7,8] as well as some thieno fused heterocycles.[7–9] In the present work we describe some other transformations of **1**.

Thus, compound **1** was found to react with acrylic acid derivatives **2a–c** in refluxing 10% ethanolic sodium hydroxide solution to afford 1:1 adducts. Analytical and spectral data showed that these products may be the *N*-alkylated derivatives **3** or the thienopyridine derivatives **4**. However, the presence of a cyano absorption band in the IR spectra of the products at $\nu \sim 2180$ cm^{-1} readily excludes the possibility of **4**. Thus structures **3a–c** were established for these products (Scheme I).

Compounds **3a–c** were refluxed in 20% ethanolic sodium hydroxide for a longer time in a trial to obtain the thienopyridine derivatives **4a–c** respectively; however, again the IR spectra of the new products were found to have a cyano absorption band at ν 2186 cm^{-1}. Furthermore, the three products obtained were found to have the same melting point. TLC analysis showed that they are one compound and that this compound has a faint acid reaction to sodium bicarbonate solution. The thiophene carboxylic acid derivative **5**-obtained presumably via hydrolysis of the *N*-alkyl and the CN groups of **3**- and the β-alanine derivative **6** were considered as structures for this product. However, our product was found to be different from **5** previously reported by us,[8] both by melting point and TLC comparison. Thus

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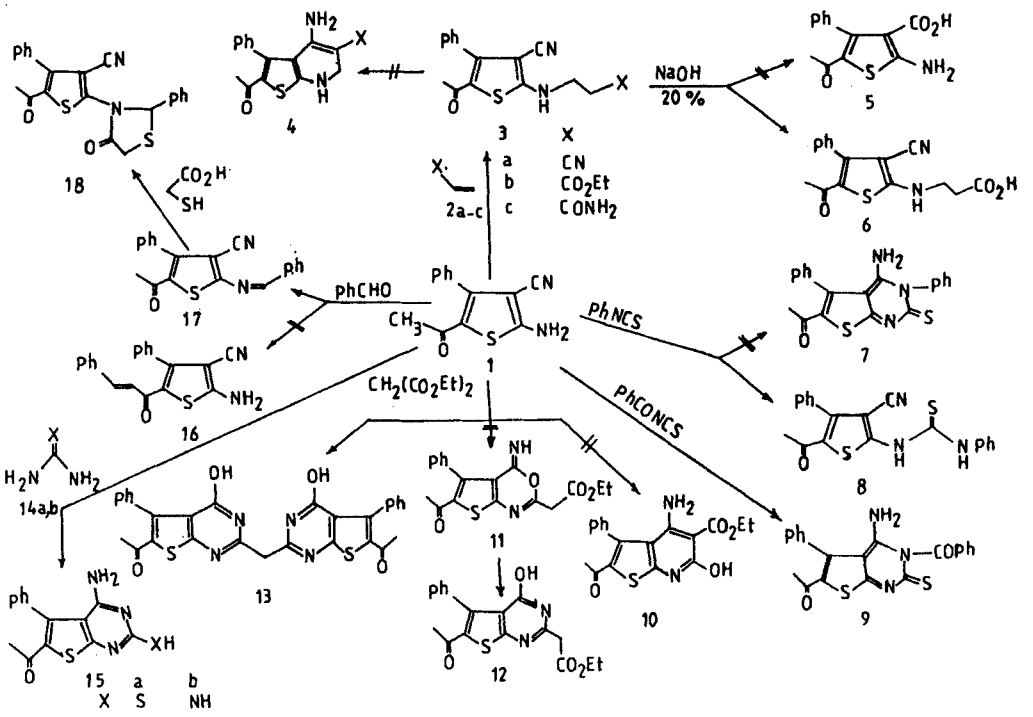

SCHEME I

structure **6** was assigned to this product. Analytical and spectral data are in accord with this structure (cf. Tables I and II).

Compound **1** reacts with phenyl isothiocyanate to afford a 1:1 adduct which was expected to be the 2,3-dihydrothienopyrimidine derivative **7**, however the *N*,*N*-disubstituted thiourea derivative **8** was instead obtained. In contrast to this, **1** reacts with benzoyl isothiocyanate in refluxing acetone to afford the 3-benzoyl-2,3-dihydrothieno[2,3-*d*]pyrimidine-2-thione derivative **9**. The IR spectrum of **9** did not show any cyano absorption band in the region of ν 2200-2170 cm^{-1}, while that of **8** revealed a cyano absorption at ν 2175 cm^{-1}.

Compound **1** reacts with diethyl malonate to afford a product which was expected to be either **10**, **11** or its rearranged **12**. The ^{1}H-NMR spectrum of the product did not reveal any signals that can be attributed to the ester CH_2CH_3 group, and the IR spectrum did not show any cyano absorption bands. It seems that both sides of the malonic ester were involved in the reaction with two moles of **1** followed by ring opening and recyclization of the formed oxazine to afford the methylene bis-thieno[2,3-*d*]pyrimidine derivative **13**. Similar behaviour of **1** towards malononitrile and ethyl cyanoacetate has been observed.[9]

Compound **1** reacts with thiourea **14a** and guanidine **14b** in refluxing methanol in presence of sodium methoxide to afford products for which the thieno[2,3-*d*]-pyrimidine structures **15a** and **15b** were assigned respectively. This structural assignment is based on analytical data as well as the absence of cyano group absorption in the IR spectra of the products which indicates the involvement of it in the reaction (Scheme I; Tables I and II).

TABLE I

Physical data of the newly prepared compounds

Compd. No.	MP °C Solvent	Yield %	M.F. M. Wt.	Analysis % Calc. / Found	C	H	N
3a	310 DMF/EtOH	69	$C_{16}H_{13}N_3OS$ 295.36	Calc.	65.06	4.44	14.23
				Found	65.0	4.5	14.6
3b	285 DMF/EtOH	60	$C_{18}H_{18}N_2O_3S$ 342.42	Calc.	63.14	5.30	8.18
				Found	63.5	5.1	8.3
3c	320 DMF/EtOH	53	$C_{16}H_{15}N_3O_2S$ 313.38	Calc.	61.32	4.82	13.41
				Found	61.1	4.5	13.2
6	215 EtOH	45	$C_{16}H_{14}N_2O_3S$ 314.36	Calc.	61.13	4.49	8.91
				Found	60.9	4.6	8.5
8	240 DMF	51	$C_{20}H_{15}N_3OS_2$ 377.49	Calc.	63.64	4.01	11.13
				Found	63.5	4.2	11.4
9	335 DMF	52	$C_{21}H_{15}N_3O_2S_2$ 405.50	Calc.	62.20	3.73	10.36
				Found	62.1	3.7	10.5
13	320 DMF	45	$C_{29}H_{20}N_4O_4S_2$ 552.63	Calc.	63.03	3.65	10.14
				Found	62.6	3.4	10.4
15a	329 DMF	53	$C_{14}H_{11}N_3OS_2$ 301.39	Calc.	55.79	3.68	13.94
				Found	56.0	4.1	14.2
15b	265 DMF	58	$C_{14}H_{12}N_4OS$ 284.34	Calc.	59.14	4.25	19.70
				Found	59.1	4.4	20.5
17	245 DMF/EtOH	78	$C_{20}H_{14}N_2OS$ 330.41	Calc.	72.70	4.27	8.48
				Found	73.1	4.6	8.9
18	140 AcOH	75	$C_{22}H_{16}N_2O_2S_2$ 404.51	Calc.	65.32	3.99	6.93
				Found	65.1	4.2	7.4

Compound **1** also undergoes condensation with benzaldehyde to afford a product which can be formulated as the chalcone **16** or the *N*-benzylidene derivative **17**. Elemental analyses seem to be of little help in discriminating **16** and **17**, however, the presence of a methyl singlet at δ 2.35 ppm in the ^{1}H-NMR spectrum of the product and the absence of NH_2 (IR, ^{1}H-NMR) confirms that the condensation took place on the amino group of **1** rather than the methyl group, and structure **17** was thus established for this product. The ^{1}H-NMR also revealed, along with the ten aromatic protons at δ 7.1–8.1 ppm, a one proton singlet at δ 5.5 ppm which can be assigned to the *N*=CH proton.

Compound **17** reacts with thioglycollic acid to afford a 1:1 adduct. The *N*-substituted thiazolidin-4-one structure **18** was assigned to this product based on spectral and analytical data (see Experimental part).

Thus some new thiophene and thieno[2,3-*d*]pyrimidine derivatives are now available from cheap and easily obtainable starting materials. The reaction procedures

TABLE II

Spectral data of the newly prepared compounds

Compd. No.	IR ν cm^{-1} (Selected bands)	^{1}H-NMR δ ppm
3a	3240(NH),2200&2185 (two CN),1673(CO).	2.1(s,3H,CH_3);2.5(t,2H,CH_2);3.4 (t,2H,CH_2);5.5(br.s,1H,NH);7.1-8.0(m,5H,arom.).
3b	3220(NH),2184(CN), 1720&1661(two CO).	1.1(t,3H,CH_3);2.15(s,3H,CH_3);2.5 (t,2H,CH_2);3.5(br.m,4H,CH_2CO+ester CH_2);5.5(br.s,1H,NH);7.1-8.1(m, 5H,arom.).
3c	3340-3180(br.,NH&NH_2), 2179(CN),1663&1650(2CO).	2.1(s,3H);2.5(t,2H);3.35(t,2H);5.52 (br.s,1H);6.4(br.s,2H);7.1-8(m,5H).
6	3505&3314(OH+NH),2186 (CN),1703&1638(two CO).	2.15(s,3H,CH_3);2.45(t,2H,CH_2);3.48 (t,2H,CH_2);5.52(br.s,1H,NH);7.15-8.1(m,5H,arom.);12.5(s,1H,acid H).
8	3440-3260(NH),2175 (CN),1650(CO).	2.3(s,3H,CH_3);6.6(br.s,1H,NH);7.3-(s,1H,NH);7.4-8.2(m,10H,arom.).
9	3445(br.NH_2),1683& 1662(two CO).	2.35(s,3H,CH_3);6.8-8.2(m,12H, arom.+NH_2).
13	3565-3380(br.OH), 1662(CO).	2.35(s,6H,$2CH_3$);3.3(s,2H,CH_2);7.35-8.25(m,12H,arom.+ two OH).
15a	3400-3150(br.NH_2), 1665(CO).	2.33(s,3H,CH_3);7.1-8.05(m,7H,arom.+ NH_2);8.6(s,1H,SH).
15b	3420-3160(br.NH_2), 1650(CO).	2.35(s,3H,CH_3);6.9-8.0(m,7H,arom.+ NH_2);8.1(s,2H,NH_2).
17	2197(CN),1661(CO).	2.35(s,3H,CH_3);5.5(s,1H,CH);7.1-8.1(m,10H,arom).
18	2185(CN),1680&1665 (two CO).	2.3(s,3H,CH_3);3.9(s,2H,CH_2);4.8(s, 1H,CH);7.25-8.1(m,10H,arom.).

and separation techniques are simple. The prepared compounds seem to be interesting for biological activity studies. Furthermore, the work describes a simple route to the hitherto unknown *N*-heterocyclic substituted β-alanine which may be useful to protein and peptide chemists.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded as 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 ppm values. Microanalyses were performed in the microanalytical center at Cairo University.

Reaction of **1** *with acrylic acid derivatives* **2a–c***: preparation of the N-alkylated 2-aminothiophene derivatives* **3a–c**. To a solution of **1** (2.42 g; 0.01 mole) in 20 ml of ethanol was added 0.01 mole of either **2a, b** or **c** followed by 5 ml of a 10% aqueous solution of sodium hydroxide. The reaction mixture was refluxed in each case for 2 h, then left to cool to room temperature. The contents of the flask were poured into ice-cold water and neutralized by hydrochloric acid. The precipitated solids were collected by filtration and recrystallized (DMF/EtOH) to afford **3a, 3b** and **3c** respectively (Tables I & II).

N-(5-acetyl-3-cyano-4-phenylthien-2-yl)-β-alanine **6**. To a solution of 0.01 mole of each of **3a, b** or **c** in 20 ml of ethanol was added 5 ml of 20% of aqueous sodium hydroxide solution. The reaction mixture was refluxed for 2 h, after which it was cooled, poured into cold water and neutralized by HCl. After filtration and recrystallization (EtOH) of the solid product obtained in each case they were found to be the same compound **6**.

N-phenyl-Ń-(5-acetyl-3-cyano-4-phenylthien-2-yl) thiourea **8**. To a solution of **1** (2.42 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 recrystallized from DMF (Tables I and II).

6-Acetyl-4-amino-3-benzoyl-5-phenyl-2,3-dihydrothieno[2,3-d]pyrimidin-2-thione **9**. To 0.01 mole of benzoyl isothiocyanate (prepared in sito from benzoyl chloride and ammonium thiocyanate) in dry acetone was added **1** (2.42 g; 0.01 mole) and the reaction mixture was refluxed for 2 h. On cooling, a solid product was separated which was filtered off and recrystallized from DMF (Tables I and II).

Methylene bis-(6-acetyl-4-hydroxy-5-phenylthieno[2,3-d]pyrimidin-2-yl) **13**. To a solution of **1** (2.42 g; 0.01 mole) in 15 ml of DMF was added diethyl malonate (0.8 g; 0.005 mole) followed by 0.5 ml of piperidine. The reaction mixture was refluxed for 2 h then left to cool overnight. The precipitated solid was filtered off and recrystallized to afford **13**.

2-Substituted-6-acetyl-5-phenylthieno[2,3-d]pyrimidine derivatives **15a, b**. To a solution of **1** (2.42 g; 0.01 mole) in 20 ml of methanol was added 0.01 mole of thiourea **14a** or guanidine nitrate **14b**, followed by sodium methoxide (one and two molar equivalents respectively). The reaction mixture was refluxed for 2–5 h (TLC control), then left to cool overnight. The precipitated solids were filtered off and recrystallized from DMF to afford **15a** and **15b** respectively.

2-(N-benzylidene) amino-5-acetyl-4-phenylthiophene-3-carbonitrile **17**. To a solution of **1** (2.42 g; 0.01 mole) in ethanol (20 ml), was added benzaldehyde (1.06 g; 0.01 mole) followed by few drops of triethylamine as catalyst. The mixture was refluxed for 2 h after which was left to cool to room temperature. The solid product that appeared was filtered off, recrystallized and characterized as **17**.

N-(5-acetyl-3-cyano-4-phenylthien-2-yl)-2-phenylthiazolidin-4-one **18**. A mixture of **17** (1.65 g; 0.005 mole) and thioglycolic acid (0.46 g; 0.005 mole) was dissolved in 10 ml of piperidinium acetate (acetic acid-piperidine 1:1). The reaction mixture was refluxed for 2 h then left to cool. On dilution with ice cold water a solid precipitate appeared which was filtered off and recrystallized to afford **18**.

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