Heterocyclic Synthesis with Nitriles: A Novel Synthesis of Some Thiophene and Thieno[2,3-d]pyrimidine Derivatives, II [1]

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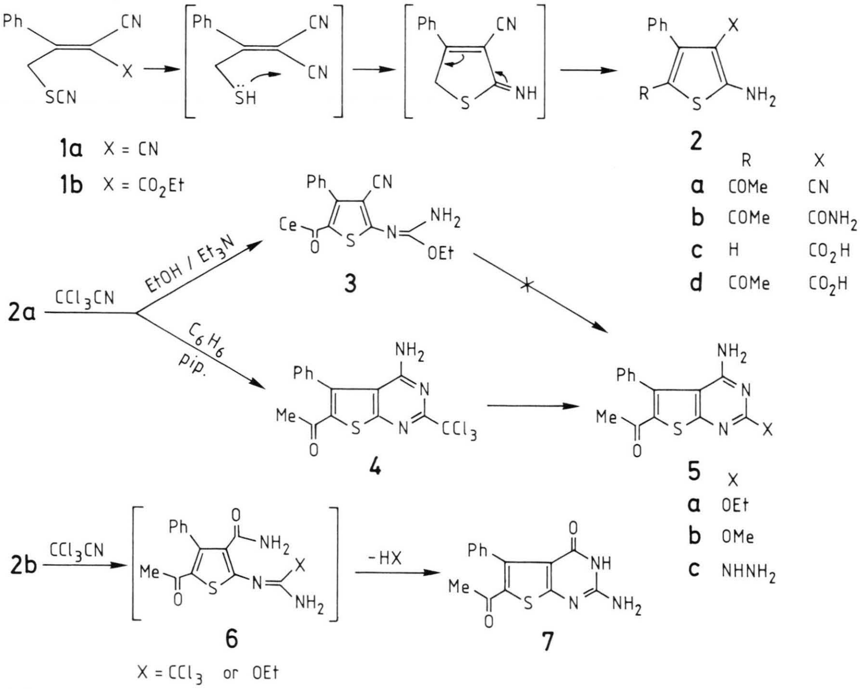
β-Thiocyanatomethyl Cinnamonitrile, Thiophene Derivatives,
Thieno[2,3-d]pyrimidine Derivatives

Some differently substituted 4-phenylthiophene derivatives **2a–d** and **8a, b** have been prepared from *α*-substituted-*β*-thiocyanatomethyl cinnamonitrile (**1**). The thiophene derivatives **2a, b** and **8a** react with trichloroacetonitrile and formamide to afford thieno[2,3-d]pyrimidine derivatives **4, 5a–c, 7** and **9a–c,** respectively.

2-Amino-3-functionally substituted thiophene derivatives are important intermediates to the pharmaceutically important thieno[2,3-d]pyrimidines [2]. These thiophene derivatives were available from the procedures published by K. Gewald [3, 4] *via* either the reaction of *α*-methylene ketones with active methylene nitriles in presence of elementary sulphur of from *α*-mercaptoketones and active methylene nitriles.

In continuation of a program aiming to develop new simple procedures for the synthesis of azoles, azines and their condensed derivatives utilizing laboratory available starting materials [5, 6], we have recently reported [1] a novel and simple synthesis of 2-aminothiophene-3-carbonitrile derivative **2a** from *α*-cyano-*β*-thiocyanatomethyl cinnamonitrile **1a** [5, 6] by refluxing the latter in acetic/sulphuric acid mixture presumably *via* the sequence shown in Scheme 1. In the present work I wish to shed more



Scheme 1.

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light on this reaction and extend it to synthesize some other thiophene derivatives as well as their reaction with trichloroacetonitrile.

As mentioned above, we have reported [1] that **1a** undergoes cyclization with acetylation in the free 5-position to afford the thiophene derivative **2a** when refluxed in acetic/sulphuric acid mixture with traces of water for 2 h. It has been actually found that the reaction product depends essentially on the reaction conditions. Thus, when the reflux time was extended to 3 h or more with the same reaction mixture, another compound was formed. The IR spectrum of this new product did not reveal any absorption bands in the region of 2250–2200 cm^{-1} that can be attributed to cyano group and instead two more protons appeared at δ 10.67 ppm in the ^1H NMR spectrum relative to that of **2a.** The IR spectrum showed also two carbonyl absorption bands at ν 1652 and 1682 cm^{-1} against one carbonyl band in that of **2a** at ν 1650 cm^{-1}. On the basis of these spectral as well as analytical data, the amide structure **2b** was assigned to this reaction product.

Compound **2b** was also obtained from **2a** upon reflux of the latter in the same reaction mixture for 1 h. The identity of the two products was deduced from m.p. and ^1H NMR spectra.

Compound **1a** was also found to afford another product when refluxed in acetic/dilute sulphuric acid mixture for 4 h. The ^1H NMR spectrum of this product did not reveal any methyl protons and instead a signal of 1H at δ 6.8 ppm and another 1H at δ 11.86 ppm assignable to thiophene 5-H and a carboxylic proton respectively. The ^{13}C NMR chart of this product confirmed the suggested structure **2c.** It revealed the thiophene C-5 at δ 98.03 ppm splitted into doublet in the off-resonance spectrum beside other three doublets assignable to the phenyl group, and three singlets one of which at δ 172.99 ppm attributed to the carboxylic C=O. On the basis of these informations, structure **2c** was established for this reaction product.

On the other hand, when compound **1a** was refluxed in an acetic/conc. sulphuric acid mixture with traces of water for 2 h, followed by addition of *ca.* 3 ml of water and reflux was continued for further 2 h, compound **2d** was formed. Structure **2d** was assigned on the basis of analytical as well as spectral data which revealed an ^1H NMR pattern similar to that of **2c** except having a methyl signal at δ 2.36 ppm and the absence of the thiophene 5-H at δ 6.8 ppm.

Compound **2d** was also obtained either from **2a** or **2b** by reflux in acetic/dilute sulphuric acid mixture for 2 h, or from **2c** by reflux in glacial acetic acid containing few drops of conc. sulphuric acid for 1 h.

As the reaction is now clearly dependant on the reaction time and the concentration of the sulphuric acid used, it has been found preferably to carry out the reaction in acetic acid/conc. hydrochloric acid mixture with a few drops of water, whenever compound **2a** is wanted. Under these conditions compound **2a** is only formed independent of the reaction time.

It has also been reported [1] that compound **2a** when allowed to react with trichloroacetonitrile in refluxing ethanol catalysed by triethylamine afforded the formamidino derivative **3,** which failed to cyclize to the thienopyrimidine derivative **5a.** It seems that the trichloromethyl moiety undergoes substitution by ethoxy group more faster than the cyclization process to the CN group, and this inhibits this process to take place. Thus it seemed to me that the use of an aprotic solvent in this reaction will prevent this substitution. Actually compound **2a** was found to react with trichloroacetonitrile in dry benzene with a catalytic amount of piperidine to afford quantitatively the thienopyrimidine derivative **4** (see Table I).

Being a good leaving group, the trichloromethyl moiety in compound **4** afforded a good facility to obtain in a very simple way other substituted thienopyrimidine derivatives. Thus, refluxing **4** in ethanol, methanol or in dioxan containing hydrazine hydrate afforded the corresponding thienopyrimidine derivatives **5a–c,** respectively. Structures of compounds **5a–c** were deduced from spectral and analytical data (Table I).

Ready substitution of the trichloromethyl moiety by nucleophilic reagents has been previously reported [5].

Compound **2b** reacts, however, with trichloroacetonitrile either in ethanol or in dry benzene to afford one and the same product for which structure **7** was assigned on the basis of spectral and analytical data (Table I). In this case the solvent has no effect on the reaction product, presumably due to the fact that the cyclization step takes place *via* elimination of HX instead of internal Michael addition in the above case. So, it seems that the nature of X whether CCl_3 or OC_2H_5 makes no difference and has no effect on

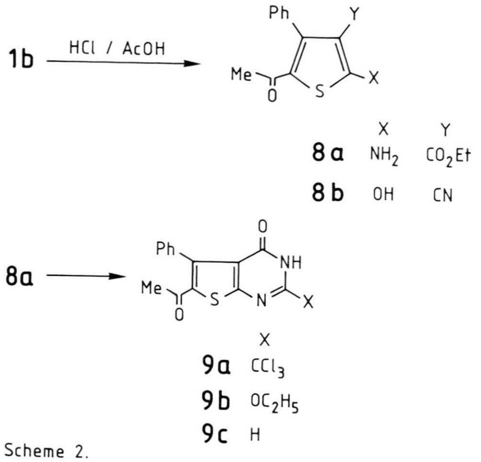
Table I. Physical and spectral data of the newly prepared compounds.

Compd. No.	Yield [%]	m.p. [°C] solvent	M.F. M.Wt.	Cd Fd	Analysis [%] C	H	N	IR [ν cm^{-1}] Selected bands	^{1}H NMR [δ ppm]
2b	76	>270 Dil. DMF	$C_{13}H_{12}N_2O_2S$ 260.32		59.98 59.45	4.65 4.83	10.76 11.00	3450–3100 (NH_2), 1682, 1652 (C=O)	2.54 (s, 3H, CH_3), 7.44–8.22 (m, 7H, Ph+NH_2), 10.67 (s, 2H, N
2c	75	197 Ethanol	$C_{11}H_9NO_2S$ 219.26		60.26 60.75	4.14 4.51	6.39 6.60	3500–3330 (br. OH), 3142 (NH_2), 1657 (C=O)	3.33 (s, 2H, NH_2), 6.8 (s, 1H, thio 5-H), 7.3–7.77 (m, 5H, Ph), 11.8 (s, 1H, COO$\underline{H}$)
2d	79	72 Ethanol	$C_{13}H_{11}NO_3S$ 261.30		59.76 60.10	4.24 4.32	5.36 5.52	3450–3320 (br. OH), 3107, 3060 (NH_2), 1656 (C=O)	2.36 (s, 3H, CH_3), 3.34 (s, 2H, NH 7.33–8.09 (m, 5H, Ph), 12.1 (s, 1 COO$\underline{H}$)
4	82	180 Benzene	$C_{15}H_{10}N_3OSCl_3$ 386.69		46.59 47.30	2.65 2.85	10.87 11.10	3120–3070 (NH_2), 1670 (C=O)	2.43 (s, 3H, CH_3), 7.31–8.15 (m, 7 Ph+NH_2)
5a	75	169 Ethanol	$C_{16}H_{15}N_3O_2S$ 313.38		61.32 60.90	4.82 5.13	13.41 13.50	3125–3080 (NH_2), 1653 (C=O)	1.05 (t, 3H, CH_3), 1.66 (s, 3H, CH 3.44 (q, 2H, CH_2), 7.22–7.83 (m, 7 Ph+NH_2)
5b	75	160 Methanol	$C_{15}H_{13}N_3O_2S$ 299.35		60.18 59.92	4.38 4.72	14.04 13.90	3329–3189 (NH_2), 1646 (C=O)	0.9 (s, 3H, CH_3), 1.3 (s, 3H, CH 7.28–7.80 (m, 7H, Ph+NH_2)
5c	74	222 Ethanol	$C_{14}H_{13}N_5OS$ 299.36		56.17 55.85	4.38 4.12	23.39 23.03	3500–3200 (br. NH+NH_2), 1650 (C=O)	2.35 (s, 3H, CH_3), 3.35 (s, 2H, NH 5.4 (s, 1H, NH), 7.15–8.1 (m, 7H Ph+NH_2)
7	81	>270 DMF	$C_{14}H_{11}N_3O_2S$ 285.33		58.93 58.57	3.89 3.68	14.73 14.43	3330–3149 (br. NH+NH_2), 1650 (br. C=O)	2.36 (s, 3H, CH_3), 3.35 (s, 2H, NH 7.33–8.0 (m, 5H, Ph), 8.08 (s, 1 NH)
8a	22	98 EtOH	$C_{15}H_{15}NO_3S$ 289.35		62.26 61.85	5.22 5.41	4.84 5.22	3320–3195 (NH_2), 1745 and 1685 (2 CO)	1.9 (t, 3H, CH_3), 2.5 (s, 3H, CH_3), 2 (q, 2H, CH_2), 7.32–7.86 (m, 7H, ar.+NH_2)
8b	45	195 EtOH	$C_{13}H_9NO_2S$ 243.29		64.18 63.92	3.73 3.82	5.76 5.80	3500–3100 (br. OH), 2195 (CN), 1690 (CO)	2.4 (s, 3H, CH_3), 7.3–7.65 (m, 5 ar.), 8.5 (s, 1H, OH)
9a	67	208 Toluen	$C_{15}H_9N_2O_2SCl_3$ 387.67		46.47 46.15	2.34 2.70	7.23 7.50	3300–3100 (NH), 1695 (br. CO)	2.42 (s, 3H, CH_3), 7.35–7.88 (m, 5 ar.), 9.95 (s, 1H, NH)
9b	82	188 EtOH	$C_{16}H_{14}N_2O_3S$ 314.36		61.13 60.75	4.49 4.59	8.91 8.62	3390–3105 (NH), 1690 (br. CO)	1.95 (t, 3H, CH_3), 2.36 (s, 3H, CH 2.65 (q, 2H, CH_2), 7.34–8.0 (m, 5 ar.), 8.75 (s, 1H, NH)
9c	63	253 DMF	$C_{14}H_{10}N_2O_2S$ 270		62.21 61.90	3.73 3.82	10.36 10.52	3220–3110 (NH), 1685 and 1675 (2 CO)	2.35 (s, 3H, CH_3), 7.3–7.74 (m, 5 ar.), 8.7 (s, 1H, pyrim. 2-H), 9.82 1H, NH)

the reaction pathway. Either $CHCl_3$ or C_2H_5OH is smoothly eliminated from the intermediate **6** to afford the final product **7.**

Compounds **2c** and **2d** did not react with trichloroacetonitrile under variety of conditions and were recovered unchanged. Apparently the presence of the free carboxylic group ortho to the amino group inhibits this reaction probably due to their presence in the zwitter ionic form.

On the other side, refluxing the cinnamonitrile **1b** [6] in acetic/hydrochloric acid mixture, a mixture of two compounds which could be easily distinguished by nacked eye was obtained. Separation of these two compounds led to a yellow crystalline product of m.p. 98 °C; and a grey crystalline solid of m.p. 195 °C. The IR spectrum of the yellow product revealed the absence of cyano absorption at 2240–2180 cm^{-1}. ^{1}H NMR showed ethoxy triplet and quartet at δ 1.9 and 2.74 ppm beside a methyl singlet at δ 2.5 ppm and aromatic multiplet 5H at 7.32–7.86 ppm. Structure **8a** was thus assigned for this product. The other product showed a CN absorption band at ν 2195 cm^{-1} in



Scheme 2.

the IR and the absence of ethoxy protons in the ^{1}H NMR spectrum. Structure **8b** was established to this product on the basis of spectral and analytical data (Scheme 2, Table I).

Compound **8a** reacts with trichloroacetonitrile in refluxing toluene catalysed by piperidine to afford a yellow solid. The ^{1}H NMR spectrum of this product revealed the disappearance of the amino and ethoxy protons and instead a 1H singlet at δ 9.95 ppm assignable to pyrimidine NH has appeared. The IR and analytical data are in full agreement with structure **9a,** which was given to this product. Refluxing **9a** in ethanol, the ethoxy derivative **9b** was obtained in a very good yield.

Compound **8a** reacts also with formamide [7] to afford a greenish product. ^{1}H NMR spectrum of this product showed the presence of the pyrimidine NH singlet at δ 9.8 ppm. IR and analytical data are in complete agreement with structure **9c** which was assigned to this product.

Thus, differently substituted 2-aminothiophene derivatives are now available from the cinnamonitriles **1a, b;** which are in turn easily obtainable from laboratory available cheap starting materials. The reaction procedures and techniques used are very simple.

Experimental

All melting points are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 580 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WH90 and WP200 spectrometers in DMSO-d_6 using TMS as internal reference. Assignments were made by correlation of the off-resonance decoupled ^{13}C NMR spectra and determination of ^{1}H chemical shifts. Elemental analyses were made in the analytical laboratory, University of Hannover and microanalytical center at Cairo University.

5-Acetyl-4-phenylthiophene derivatives **2a** *and* **8a, b**

To a solution of 0.01 mole of **1a** or **1b** in 25 ml of glacial acetic acid was added 5 ml of conc. hydrochloric acid and 5 drops of water. The reaction mixture was refluxed for 3 h, then left to cool at room temperature. The resulting clear solution in each case was poured on crushed ice (*ca.* 100 g), and neutralized with ammonia solution. The precipitated solids were filtered off and recrystallized to afford 1.8 g (74%) of compound **2a,** m.p. 211 °C (reported 212 °C) [1], and 1.85 g (68% of **1b**) of a mixture of two compounds which were separated by warming the mixture in chloroform and filteration. On evaporation of the chloroform solution under reduced pressure, a yellow crystalline solid was obtained, recrystallized to afford 0.6 g of **8a.** The solid residue remaining after filteration was recrystallized from ethanol to afford 1.2 g of **8b.**

5-Acetyl-2-amino-4-phenylthiophene-3-carboxamide (**2b**)

To a solution of 2.25 g (0.01 mole) of **1a** in 25 ml of glacial acetic acid was added 2 ml of conc. sulphuric acid and 1 ml of water. The reaction mixture was refluxed for 3 h. After cooling to r.t., the light yellow coloured solution was poured on crushed ice and neutralized with ammonia solution. The precipitated yellow solid was filtered and recrystallized to give 1.95 g of **2b.**

2-Amino-4-phenylthiophene-3-carboxylic acid (**2c**)

To a solution of 2.25 g (0.01 mole) of **1a** in 25 ml of acetic acid was added 5 ml of 2 N H_2SO_4. The mixture was refluxed for 3 h. After cooling and normal treatment, the solid obtained was filtered and recrystallized to afford 1.6 g of **2c** as grey needles. ^{13}C NMR: 98.03 (d), 124.91 (d), 128.43 (d), 128.79 (d), 129.73 (s), 133.95 (s), 172.99 (s).

5-Acetyl-2-amino-4-phenylthiophene-3-caroxylic acid (**2d**)

To a solution of 2.25 g (0.01 mole) of **1a** in 25 ml of acetic acid was added 2 ml of conc. H_2SO_4 followed by 3 drops of water. The reaction mixture was refluxed for 2 h after which 3 ml of water were added and reflux continued for further 2 h. After cooling and treatment of the clear solution 2 g of **2d** was obtained as yellow crystalline solid.

6-Acetyl-5-phenyl-2-trichloromethylthieno-[2,3-d]pyrimidine derivatives **4** *and* **9a**

To a solution of 0.01 mole of **2a** or **8a** in 30 ml of dry benzene was added 1 ml (0.01 mole) of trichloroacetonitrile followed by 3 drops of piperidine as catalyst. The mixture was refluxed for 2 h, after which was cooled overnight. The crystalline solid obtained in each case was filtered and recrystallized to afford 3.1 g of **4** and 2.6 g of **9a,** respectively.

6-Acetyl-5-phenyl-2-substituted thieno-[2,3-d]pyrimidine derivatives **5a–c** *and* **9b** *(general procedure)*

0.005 mole of compounds **4** or **9a** were refluxed in absolute ethanol, methanol for 1 h, or in 20 ml of dioxan containing excess (2 ml) of hydrazine hydrate for 3 h. The solution obtained in each case was filtered while hot for recrystallization. The solids precipitated after cooling or dilution with ice-cold water were filtered to give 1.2 g of **5a,** 1.1 g of **5b,** 1.1 g of **5c** and 1.3 g of **9b,** respectively.

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

To a solution of 2.6 g (0.01 mole) of **2b** in 25 ml of ethanol catalysed by triethylamine or in 25 ml of dry benzene catalysed by piperidine was added 1 ml (0.01 mole) of trichloroacetonitrile. The reaction mixture was refluxed in either case for 2 h, then left to cool overnight. The precipitated solid in either case was filtered off and recrystallized from DMF to afford 2.3 g of **7.**

6-Acetyl-5-phenyl-3,4-dihydrothieno-[2,3-d]pyrimidin-4-one (**9c**)

A solution of **8a** (2.89 g; 0.01 mole) in 25 ml of formamide was refluxed for 2 h at which time the colour darkens. After cooling to r.t., the precipitated solid was filtered off and recrystallized to afford 1.7 g of **9c.**

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