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Procedures and Data

Heterocyclic Synthesis with Nitriles: Synthesis of some Novel Pyrrolo [2,1-*b*]thiadiazoline, Pyrrolo[2,1-*b*]thiadiazolo[3,2-*a*]pyrimidine and Pyridine Derivatives [1])

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Dedicated to Prof. Dr. N. A. Kassab on the Occasion of his 60th Birthday

Abstract. α-(Bromothiocyanatomethyl)benzylidenemalononitrile (**1**) reacts with the hydrazides **2a–c**, cyanoacetohydrazide (**2d**), cyanoacetamide (**3a**) and cyanoacetanilides **3b–d** to afford pyrrolo[2,1-*b*]thiadiazolines **5a–c**, pyrrolo[2,1-*b*]thia-diazolo[3,2-*a*]pyrimidine (**8**) and the pyridone derivatives **11a–d**. Structures and conceivable mechanisms are discussed.

Syntheses of pyrroles and fused pyrroles are known [1, 2]. We reported on approaches to pyrrole derivatives that can be used as biodegradable agrochemicals [3–7] and on the synthesis and reactions of α-(bromothiocyanatomethyl)benzylidenemalononitrile (**1**) [8, 9]. Thiadiazoles fused to heterocyclic system possess also antimicrobial activity [10]. Now we describe further reactions of **1**.-

In boiling ethanol in the presence of potassium carbonate **1** and hydrazides **2a–c** *via* assumed intermediates **4** (Scheme 1) yield pyrrolothiadiazoline imines **5a–c** and not, like **1** and phenylhydrazine alone [8], pyridazines **7**. In the IR spectra of **5a–c** no ν(SCN) was detectable, ^{1}H and ^{13}C NMR data agree with the structures **5**. Similar cyclizations to the SCN to afford imino thiadiazoles are known [11]. In ethanolic HCl **5a–c** are easily transformed into **6a–c**, elemental analyses and spectral data proved the structures **6a–c**. If **1** reacts with cyanoacetohydrazide (**2d**), further cyclization of **5** (R = $COCH_2CN$) affords the pyrrolothiadiazolopyrimidine **8**; elemental analyses and spectral data agree with structure **8**.

The reaction of **1** with cyanoacetamide and cyanoacetanilides **3a–d** takes another route. Most likely amides **3** undergoe a Michael type addition, paralleled or followed by a reverse reaction with loss of $BrCH_2SCN$ to afford the intermediate **10** (Scheme 2), and cyclization to the pyridone derivatives **11a–d**. The IR spectra of **11a–d** show two ν(CN) at 2202 and 2206 cm^{-1} and ν(CO) at 1660–1680 cm^{-1}; elemental analyses and ^{1}H NMR spectra agree with the structures **11a–d**. Under the same conditions benzylidene malononitrile **9** reacts with cyanoacetamide **3a** to give a product identical with **11a** from **1**.

Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 using TMS as internal standard. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out by the Microanalytical Center at Cairo University.

The α-(bromothiocyanatomethyl)benzylidenemalononitrile (**1**) was prepared according to the previously reported procedure [8]. – ^{13}C NMR: δ/ppm = ([$^2H_6$]DMSO) 133.66 (C-1), 131.91 (C-2), 128.50–129.69 (aromatic-C), 117.11 (CN), 116.23 (CN), 112.0 (SCN), 34.42 (C-3).

Reaction of α-(Bromothiocyanatomethyl)benzylidenemalononitrile (1) with Hydrazides 2a–c, Cyanoacetohydrazide (2d), Cyanoacetamide (3a) and Cyanoacetanilides 3b–d (General Procedure)

To (3.04 g 0.01 mol) of **1** and 0.01 mol of each of **2a–c**, **2d**, **3a** or **3b–d** in ethanol (30 ml) was added a solution of potassium carbonate (1.38 g, 0.01 mol) in a minimum amount of water, and refluxed for 3–5 h (T. L. C control). The mixture was left to cool overnight, poured in cold water, and neutralized with HCl. The dark precipitates that appeared were separated by filtration and recrystallized.

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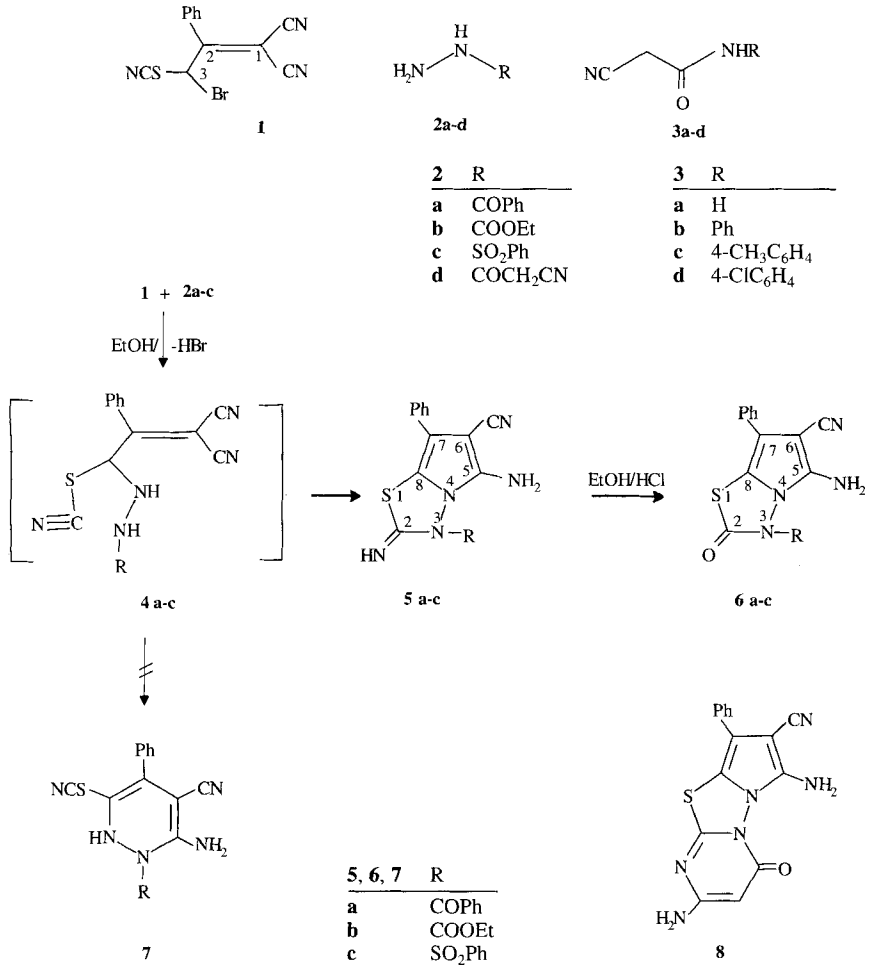
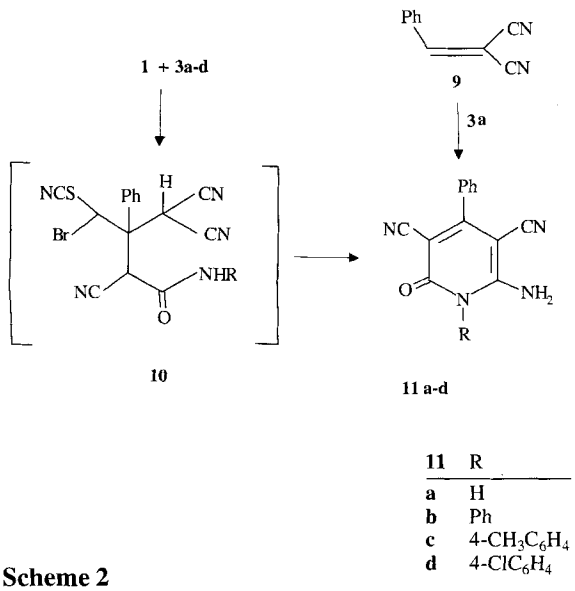


Scheme 1



Scheme 2

5-Amino-3-benzoyl-6-cyano-7-phenylpyrrolo[2,1-b]thiadiazoline-2-imine (**5a**)

5a: 85% yield; *m.p.* > 330 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3423–3200 (NH_2 and NH), 2206 (CN) and 1687 (hydrogen bonded C=O). – ^1H NMR ([$^2H_6$] DMSO): δ/ppm = 7.2 – 8.0 (m, 10H), 8.18 (s, 2H) and 11.40 (s, 1H). – ^{13}C NMR ([$^2H_6$] DMSO): δ/ppm = 172.53 (CO), 165.3 (C-2), 156.34 (C-5), 145.04 (C-8), 134 (C-6), 126.24-133.4 (aromatic-C), 117.1 (CN) and 109.13 (C-7). – MS: *m/e* (%) 359.

$C_{19}H_{13}N_5OS$	Calcd.:	C 63.47	H 3.64	N 19.49
(359.22)	Found:	C 63.73	H 3.84	N 19.70.

5-Amino -6-cyano-3-ethoxycarbonyl-7-phenylpyrrolo [2,1-b]thiadiazoline-2-imine (**5b**)

5b: 63% yield; *m.p.* > 300 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3423–3200 (NH_2 and NH), 2205 (CN) and 1713 (hydrogen bonded ester C=O). – ^1H NMR ([$^2H_6$] DMSO): δ/ppm = 1.3 (t, 3H), 2.41 (q, 2H), 7.2–7.81 (m, 5H), 8.25 (s, br., 2H) and 11.3 (s, 1H). – MS: *m/e* (%) 327.

$C_{15}H_{13}N_5O_2S$	Calcd.:	C 55.01	H 4.00	N 21.40
(327.21)	Found:	C 55.25	H 3.76	N 21.70.

5-Amino-3-benzenesulfonyl-6-cyano-7-phenylpyrrolo [2,1-b]thiadiazoline-2-imine (**5c**)

5c: 72% yield; *m.p.* > 300 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3423–3200 (NH_2 and NH) and 2206 (CN). – ^1H NMR

([$^2H_6$] DMSO): δ/ppm = 7.2–8.1 (m, 10H), 8.31 (s, 2H) and 11.4 (s, 1H). – MS: *m/e* (%) 395.

$C_{18}H_{13}N_5O_2S_2$	Calcd.:	C 54.64	H 3.31	N 17.72
(395.27)	Found:	C 54.91	H 3.55	N 17.50.

2,5 -Diamino-6-cyano-7-phenylpyrrolo[2,1-b]thiadiazolo[3,2-a]pyrimidin-4-one (**8**)

8: 94% yield; *m.p.* > 300 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3400–3230 (NH_2), 2205 (CN) and 1650 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 7.2–7.7 (m, 6H), 8.2 (s, 2H) and 8.4 (s, 2H). – MS: *m/e* (%) 322.

$C_{15}H_{10}N_6OS$	Calcd.:	C 55.87	H 3.12	N 26.08
(322.19)	Found:	C 55.60	H 3.38	N 26.30.

2-Amino-3,5-dicyano-4-phenyl[1,6]dihydropyridin-6-one (**11a**)

11a: 86% yield; *m.p.* > 268 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3400–3200 (NH_2) and 2205 (CN), 2202 (CN) and 1680 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 7.21–8.2 (m, 7H) and 10.4 (s, 1H). – MS: *m/e* (%) 236.

$C_{13}H_8N_4O$	Calcd.:	C 66.07	H 3.41	N 23.72
(236.10)	Found:	C 66.37	H 3.11	N 23.60.

2-Amino-3,5-dicyano-1,4-diphenyl[1,6]dihydropyridin-6-one (**11b**)

11b: 95% yield; *m.p.* 190 °C (EtOH). – IR: ν/cm^{-1} = 3400–3200 (NH_2) and 2206 (CN), 2204 (CN) and 1681 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 7.22–8.4 (m, 12 H). – MS: *m/e* (%) 312.

$C_{19}H_{12}N_4O$	Calcd.:	C 73.05	H 3.87	N 17.94
(312.14)	Found:	C 73.25	H 3.67	N 18.20.

2-Amino-3,5-dicyano-4-phenyl-1-(4-methylphenyl)[1,6]dihydropyridin-6-one (**11c**)

11c: 97% yield; *m.p.* 205 °C (EtOH). – IR: ν/cm^{-1} = 3400–3200 (NH_2) and 2206 (CN), 2204 (CN) and 1680 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 2.4 (s, 3H), 7.1–8.22 (m, 11 H). – MS: *m/e* (%) 326.

$C_{20}H_{14}N_4O$	Calcd.:	C 73.59	H 4.32	N 17.17
(326.15)	Found:	C 73.74	H 4.12	N 17.30.

2-Amino-3,5-dicyano-1-(4-chlorophenyl)-4-phenyl[1,6]dihydropyridin-6-one (**11d**)

11d: 98% yield; *m.p.* 210 °C (EtOH). – IR: ν/cm^{-1} = 3400–3200 (NH_2) and 2206 (CN), 2204 (CN) and 1683 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 7.1–8.3 (m, 11H). – MS: *m/e* (%) 347.

$C_{19}H_{11}N_4OCl$	Calcd.:	C 65.79	H 3.19	N 16.16
((346.58)	Found:	C 65.40	H 3.35	N 16.38.

Conversion of 5a–c into 6a–c

In ethanolic HCl (30 ml) was added 1 g of each of **5a–c**, the reaction mixture was refluxed for 4 hr, left to cool, then filtered off. The solid so obtained was crystallised:

5-Amino-3-benzoyl-6-cyano-7-phenylpyrrolo[2,1-b]thiadiazolin-2-one (**6a**)

6a: 80% yield; *m.p.* > 300 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3400–3200 (NH_2), 2206 (CN), 1687 (hydrogen bonded C=O) and 1650 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 7.2–8.1 (m, 10H), 8.2 (s, 2H) and 11.5 (s, 1H). – ^{13}C NMR ([$^2H_6$] DMSO): δ/ppm = 175.2 (C-2), 171.68 (CO), 156 (C-5), 147 (C-8), 135.2 (C-6), 126.05-133 (aromatic-C), 117.2 (CN) and 109.5 (C-7). – MS: *m/e* (%) 360.

$C_{19}H_{12}N_4O_2S$	Calcd.:	C 63.30	H 3.35	N 15.55
(360.19)	Found:	C 63.50	H 3.18	N 15.70.

5-Amino-6-cyano-3-ethoxycarbonyl-7-phenylpyrrolo[2,1-b]thiadiazolin-2-one (**6b**)

6b: 60% yield; *m.p.* 290 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3400–3200 (NH_2), 2205 (CN) and 1713 (hydrogen bonded ester C=O) , 1655 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 1.3 (t, 3H), 2.4 (q, 2H), 7.2–7.82 (m, 5H), 8.31 (s, br., 2H) and 11.3 (s, 1H). – MS: *m/e* (%) 328.

$C_{15}H_{12}N_4O_3S$	Calcd.:	C 54.85	H 3.68	N 17.07
(328.19)	Found:	C 54.60	H 3.82	N 17.30.

5-Amino-3-benzenesulfonyl-6-cyano-7-phenylpyrrolo[2,1-b]thiadiazolin-2-one (**6c**)

6c: 76% yield; *m.p.* 310 °C (DMF/EtOH). – IR: ν/cm^{-1} = 3400–3200 (NH_2) and 2206 (CN), 1660 (C=O). – ^{1}H NMR ([$^2H_6$] DMSO): δ/ppm = 7.23–8.2 (m, 10H), 8.41 (s, 2H) and 11.4 (s, 1H). – MS: *m/e* (%) 396.

$C_{18}H_{12}N_4O_3S_2$	Calcd.:	C 54.51	H 3.05	N 14.13
(396.25)	Found:	C 54.70	H 3.31	N 14.4.

2-Amino-3,5-dicyano-4-phenyl[1,6]dihydro-pyridine-6-one (**11a**)

To **9** (0.01 mol) and **3a** (0.01 mol) in 30 ml of ethanol was added a solution of potassium carbonate (1.38 g, 0.01 mol) in a minimum amount of water and refluxed for 4 h. The mixture was left to cool overnight, poured on cold water and neutralized with HCl. The precipitate was recrystallized from DMF/EtOH: **11a**, yield, (1.2 g, 85%), *m.p.* 270 °C.

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