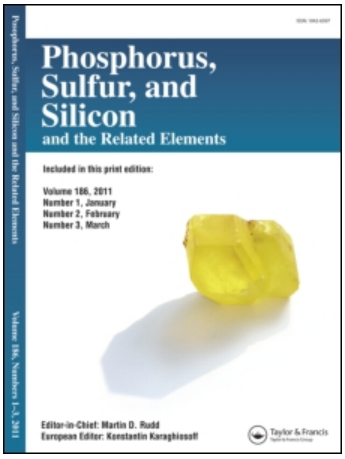

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HETEROCYCLES SYNTHESIS THROUGH REACTIONS OF NUCLEOPHILES WITH ACRYLONITRILES, PART 5, SYNTHESIS OF SEVERAL NEW THIAZOLE AND THIAZOLO[2,3-*a*]PYRIDINE DERIVATIVES

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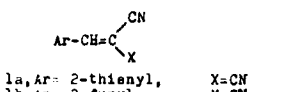
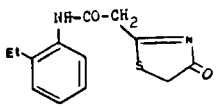
Several new thiazole and thiazolo[2,3-a]pyridine derivatives were prepared by reaction of the thiazolin-4-one derivatives **2** (synthesised from α-cyano-2-ethylacetanilide and thioglycollic acid) with acrylonitriles **1a–h**.

Key words: α-cyano-2-ethylacetanilide, acrylonitriles, 4-thiazolones, thiazolindenes, ylidene thiazolone, thiazolo[2,3-a]pyridines.

α,β-Unsaturated nitriles have recently been utilised extensively for the synthesis of a variety of heterocycles.[1–4] In previous work from our laboratory we have reported several new approaches for the synthesis of heterocycles utilizing polyfunctionally substituted nitriles as starting materials.[5,6] Thiazole derivatives find a variety of applications as bacteriostatics,[7] antibiotics,[8] CNS regulants and high ceiling diuretics.[9] Now as part of our programme directed for synthesising new polyfunctionally substituted heterocycles of expected antischistosomal activity. Thus we have investigated the possible utility of the reaction of α,β-unsaturated nitriles **1a–h** with the 4-thiazolone **2** for synthesising thiazolindenes. Reaction of thioglycollic acid with α-cyano-2-ethylacetanilide in refluxing pyridines gives the thiazolone **2** in 78% yield. Synthesis of thiazoles from nitriles via similar procedure has been reported earlier.[10] It has been found also that the reaction of **1a–h** with **2** depends on the nature of the substituent on **1**. Thus, whereas **1a–c** reacted with **2** to yield the thiazolo[2,3-a] pyridines **3a–c**, it reacted with **1d** to yield the ylidene thiazolone **4**.



1a, Ar= 2-thienyl,	X=CN
1b, Ar= 2-furyl,	X=CN
1c, Ar= 1-naphthyl,	X=CN
1d, Ar= 2-indolidonyl	X=CN
1e, Ar= 2-thienyl,	X=CO_2Et
1f, Ar= 2-furyl,	X=CO_2Et
1g, Ar= 2-thienyl,	X=COPh
1h, Ar= 2-furyl,	X=COPh



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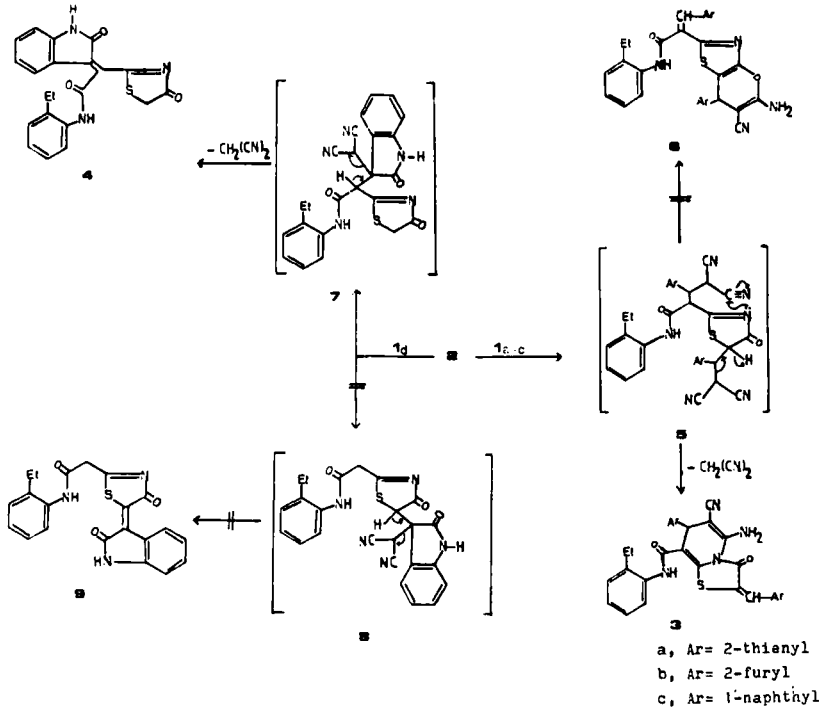
† Author to whom all correspondence should be addressed.



The formation of **3a–c** is assumed to proceed via the 1:2 adduct **5** which then undergoes cyclization and elimination of malononitrile molecule. Structure **6** as another possible isomeric structure for the reaction product was readily eliminated based on the IR spectra of the isolated products which revealed the presence of ring CO which is expected to disappear in case of **6**. The behaviour of **1a–c**

TABLE I

Analytical data of the prepared compounds

Compound no.	M.P. °C (solvent)	Yield (%) (colour)	Mol. formula (M.Wt)	Analysis (calcd/found)			
				C	H	N	S
3a	248–250	70	$C_{26}H_{20}N_4O_2S_3$	60.46	3.87	10.85	18.60
	(benzene)	(Yellow)	(516)	60.30	3.50	10.60	18.40
3b	280	72	$C_{26}H_{20}N_4O_4S$	64.46	4.13	11.57	6.61
	(EtOH)	(Brown)	(484)	64.20	3.90	11.40	6.50
3c	265–267	68	$C_{38}H_{28}N_4O_2S$	75.49	4.63	9.27	5.29
	(AcOH)	(Yellow)	(604)	75.20	4.30	9.10	5.10
4	280	65	$C_{21}H_{17}N_3O_3S$	64.45	4.34	10.74	8.18
	(DMF/H_2O)	(Red)	(391)	64.20	4.10	10.50	8.10
10a	252–254	75	$C_{21}H_{17}N_3O_3S_2$	59.57	4.01	9.92	15.13
	(EtOH)	(Yellow)	(423)	59.50	3.90	9.10	15.10
10b	204–206	72	$C_{21}H_{17}N_3O_4S$	61.91	4.17	10.31	7.86
	(EtOH)	(Brown)	(407)	61.70	4.00	10.10	7.70
12a	252–254	70	$C_{18}H_{16}N_2O_2S_2$	60.47	4.49	7.86	17.97
	(EtOH)	(Yellow)	(356)	60.20	4.10	7.60	17.70
12b	242–244	67	$C_{18}H_{16}N_2O_3S$	63.52	4.70	8.23	9.41
	(EtOH)	(Brown)	(340)	63.20	4.50	8.10	9.20

TABLE II

Spectral data of the prepared compounds

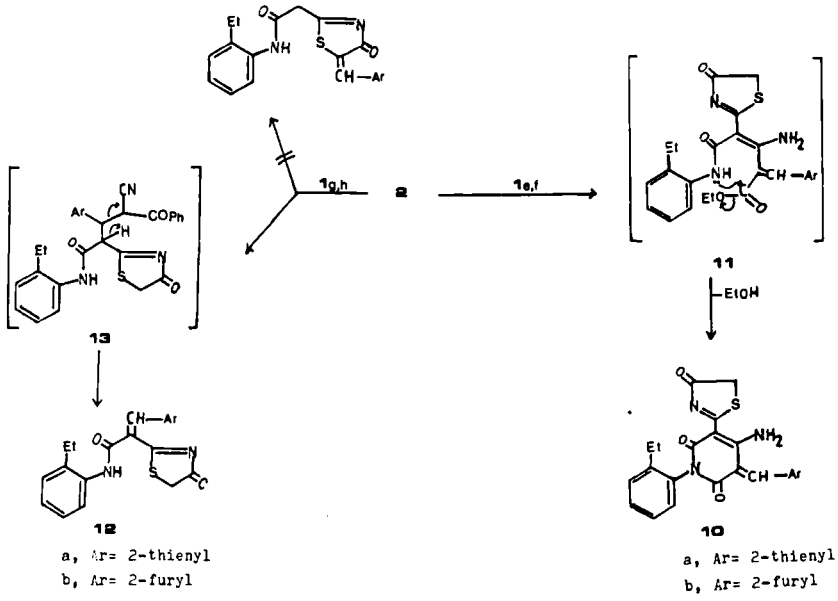
Compound no.	IR (cm^{-1})	^{1}H-nmr (δ ppm)	M^+
3a	br, 3400–3300(NH_2, NH), 2200(CN), 1710, 1670(CO)	1.2(t, 3H, CH_3), 2.8(q, 2H, CH_2),4.4(s, 1H, pyridine H-4), 5.0(br, s, 2H, NH_2), 6.7–7.0(m, 7H, thiophene protons and CH), 7.4–7.7(m, 5H, phenyl and NH protons)	516
3b	br, 3450–3250(NH_2, NH), 2200(CN), 1710, 1680(CO)	Insoluble in the available ^{1}H-nmr solvents	484
3c	br, 3400–3320(NH_2, NH), 2200(CN), 1715, 1670(CO)	—	—
4	br, 3350–3220(NH), 1715 1680(CO)	1.2(t, 3H, CH_3), 2.8(q, 2H, CH_2), 6.1 (s, 2H, CH_2), 7.5–8.0(m, 10H, Ar and NH protons)	—
10a	br, 3400–3350(NH_2), 1680 1660(CO)	1.2(t, 3H, CH_3), 2.8(q, 2H, CH_2), 4.4(s, 1H, CH), 5.4(br, s, 2H, NH_2), 6.1(s,2H, thiazole protons), 6.5–7.4(m, 7H, thienyl protons + Ar-protons)	423
10b	br, 3400–3250(NH_2), 1670 1660(CO), 1620(C = N)	Insoluble in the available ^{1}H-nmr solvent	—
12a	br, 3300–3200(NH), br, 1710–1690(CO)	1.2(t, 3H, CH_3), 2.8(q, 2H, CH_2), 6.2(s, 2H, CH_2, thiazole protons), 6.6–6.9(m,4H, thiophene protons and CH), 7.4–8.0(m,5H,Ar and NH protons)	
12b	br, 3350–3200(NH), 1710 1680(CO)	1.2(t, 3H, CH_3), 2.8(q, 2H, CH_2), 6.1(s, 2H, CH_2, thiazole protons), 6.6–6.9(m,4H, furan protons and CH), 7.4–8.0(m, 5H, Ar and NH protons)	—

toward **2** is similar to the previously reported behaviour of α,β-unsaturated nitriles toward 2-functionally substituted alkylthiazolin-4-ones.[10] Attempts to effect reaction of **1d** with **2** to yield the corresponding thiazolopyridine resulted only in the formation of the ylidene derivative **4**. The isomeric structure **9** for the reaction product was ruled out based on the presence of ring CO absorption band in the IR spectrum of the reaction product at almost the same frequency of ring CO in **2**.

In contrast to the reported formation of thiazolo[2,3-a]pyridines from reaction of ethyl ylidenecyanoacetates and 2-functionally substituted alkylthiazolin-4-ones[10] we have found that **1e, f** reacted with **2** to yield the (thiazolin-4-one)yl-pyridine **10.** The formation of **10** is assumed to proceed via addition of **2** to the cyano function in **1e, f** to yield **11** which then cyclizes to **10** by ethanol elimination. The IR spectra of **10** gives a clue for such structure showing the absence of any absorptions in the CN region (cf. Tables I,II).

The difference in behaviour of **2** toward **1e, f** may be attributed to steric consideration which makes the transition state leading to Michael adducts more energy demanding. Reaction took place thus via the less sterically hindered attack at CN function.

Similarly **12a** and **12b** are formed by reaction of **2** with **1g** and **1h** respectively.



EXPERIMENTAL

All melting points are uncorrected. the IR spectra were recorded (KBr) on a Shimadzo 408 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian A-60 spectrometer and chemical shifts are expressed in δ ppm using TMS as the internal standard. Mass spectra were recorded on mass spectrometer Finnigan MAT 8430. Analytical data were obtained from the microanalytical data unit at Cairo University.

Synthesis of α-cyano-2-ethylacetanilide. Equimolar amounts (0.01 mole) of each of o-ethylaniline and ethyl-cyanoacetate were heated in an oil bath for 1 h, then left to cool. The solid so formed was crystallized from ethanol to yield colourless crystals, m.p. 120°C.

Synthesis of 4-thiazolinone **2.** Equimolar amounts (0.01 mole) of α-cyano-2-ethylacetanilide and thioglycollic acid in pyridine (50 ml) were heated under reflux for 3 hrs. The solvent was evaporated and the remaining solid product was filtered, washed with little ethanol and then crystallized from ethanol as buff crystals m.p. 113–115°C, yield 69%.

General procedure for the reaction of **1a–h** *with* **2.** A mixture of an equimolar amounts (0.01 mole) of **1a–h** and **2** in pyridine (50 ml) was heated until the reaction was complete (tlc control). The solvent was evaporated and the remaining solid product filtered, washed with ethanol and then crystallized from the proper solvent (cf. Table I).

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