Activated Nitriles in Heterocyclic Synthesis: The Reaction of Nitriles with Mercapto Acides

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α-Mercaptocinnamic Acid, 2-Anilinomethyl-2-thiazolin-4-ones, Thiazolo[2,3-a]pyridines

Several new thiazolo[2,3-a]pyridine derivatives were obtained *via* the reaction of mercaptocinnamic acid and thioglycollic acid with some activated nitriles and treatment of the resulting 2-thiazolin-4-ones with cinnamonitrile derivatives.

As a part of our programe directed for development of new simple and efficient procedures for the synthesis of azoles and fused azoles of potential biological activity [1, 2] we have recently reported a new procedure for synthesis of 2-thiazolin-4-ones *via* the reaction of thioglycollic acid with a variety of activated nitriles [3, 4]. The chemistry of the synthesised thiazoles has also been investigated. The interesting antiinflammatory [5] and antibacterial activity [6] of the synthesised compounds prompted further interest in the synthesis and chemistry of this class of compounds. In the present paper we report on the utility of the reaction of mercaptocinnamic acid (**1**) with nitriles for the synthesis of thiazoles. Moreover, the results of our work aimed to define the scope and limitation of our procedure for synthesis of thiazoles is also reported.

Thus, it has been found that **1** reacts with malononitrile to yield a product for which structure **2** or isomeric **3** seemed possible. Structure **3** could be readily established for the reaction product based on the identity of its reaction product with benzylidenemalononitrile with authentic speciment of the thiazolo[2,3-a]pyridine (**4**) [7]. If the reaction product was **2** it would be very difficult to account for the formation of **4** in this reaction. Compound **3**, having an active methylene group, reacted with benzaldehyde to yield the arylidene bis derivative **5**.

Similar to its behaviour towards malononitrile compound **1** reacted with ethyl cyanoacetate to yield the thiazolinone derivative **6**. The structure of **6** was confirmed *via* its conversion into **7** on treatment with benzylidenemalononitrile.

Compound **1** also reacted with benzylidenemalononitrile in ethanol in the presence of catalytic amount of piperidine to yield a 1 : 1 adduct. Several isomeric structures seemed possible for the reaction product (*cf.* structures **8** and **9**). Structure **9** was established for the reaction product based on ^{1}H NMR which revealed a pattern that can only be intelligably interpretted in terms of structure **9**. Moreover, compound **9** could be converted into **11** on reflux in acetic acid. If this product is the result of cyclisation of **8** it would have structure **10**. The ^{1}H NMR of the product revealed the presence of a signal at δ 3–5 ppm for H–2 of a tetrahydrothiophen derivative.

The reactivity of cyanoacetanilide toward the action of thioglycollic acid was also investigated. It has been found that compound **12** reacts with thioglycollic acid to yield the thiazolin-4-one (**14**) which formed probably via the intermediate **13**. Compound **14**, so obtained, could be utilised for synthesis of thiazolo[2,3-a]pyridines. Thus, it reacted with benzylidenemalononitrile to yield a product of molecular formula $C_{28}H_{18}N_4O_2S$. Three isomeric structures seemed possible for the reaction product (*cf.* structures **15–17**). The pyrano[2,3-d]thiazole structure **16** was readily eliminated based on the stability of the reaction product toward the action of aqueous sodium hydroxide solution. The ^{1}H NMR spectrum of the product could be utilised to establish the thiazolo[2,3-a]pyridine structure **15** as it revealed a signal at δ 4.6 ppm for pyridine H–4.

Similar to the reactivity depicted above, compound **14** reacted with ethyl benzylidenecyanoacetate to yield the thiazolo-[2,3-a]pyridine deriva-

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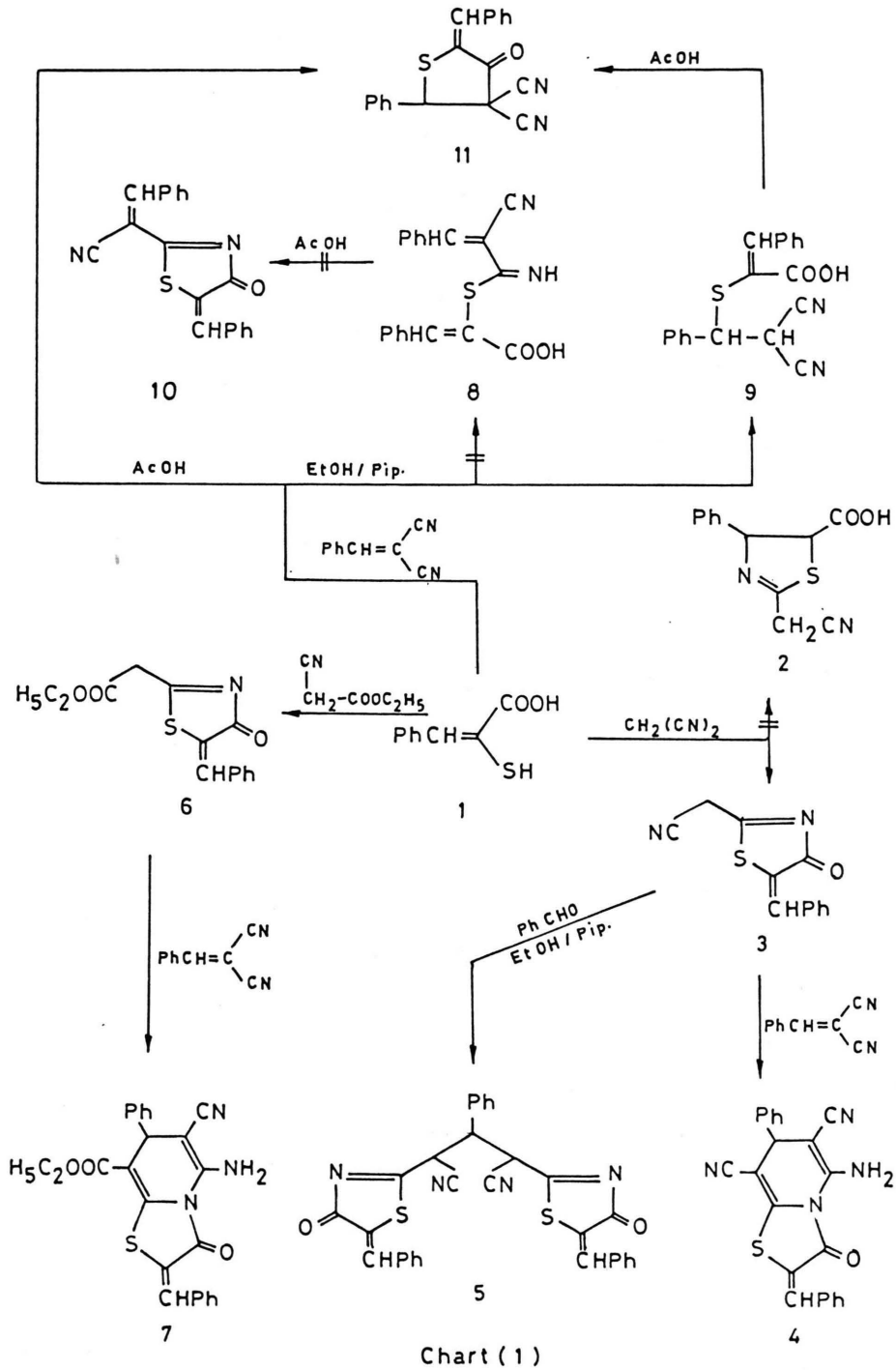

tive **18**. In contrast, the dibenzylidene derivative **19** was obtained on reacting **14** with benzoylacetonitrile. The behaviour of **14** toward activated nitriles finds parallellism to the recently reported behaviour of 2-cyanomethyl-2-thiazolin-4-one toward the same reagents by one of us [7].

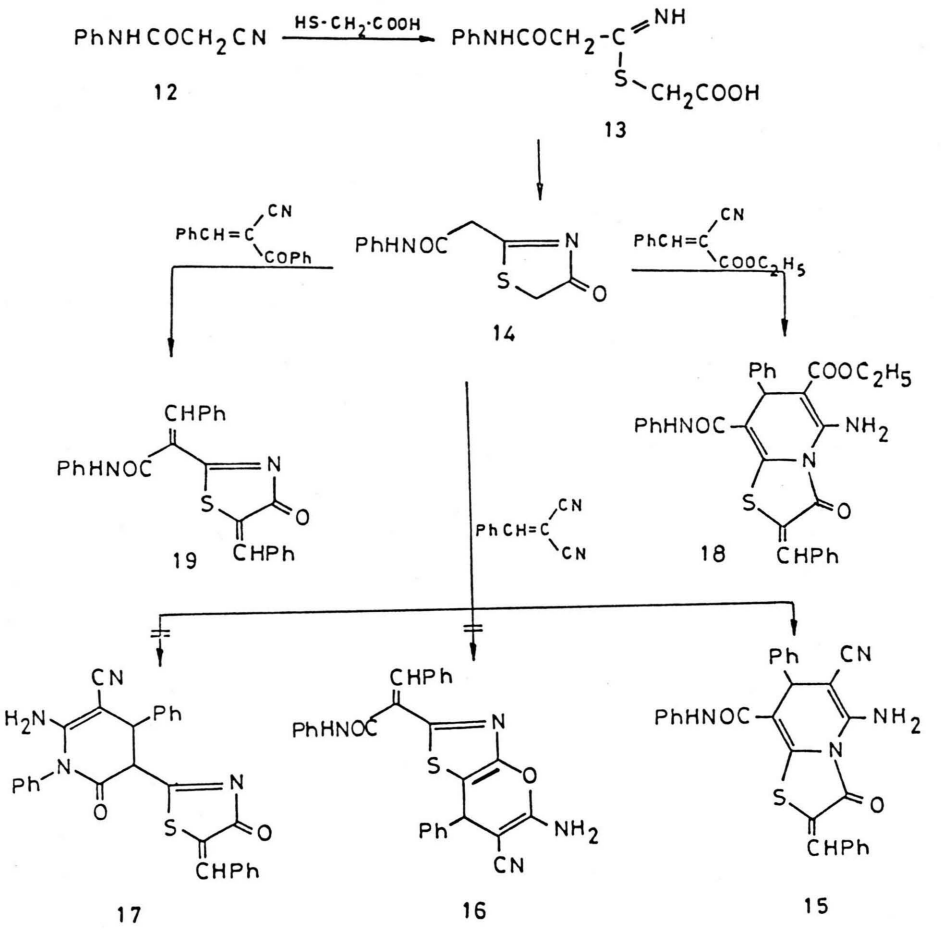

Chart (2)

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1100 spectrophotometer. ^{1}H–NMR spectra were recorded on a Varian EM-360-60 MHz spectrometer with DMSO as solvent and TMS as internal reference. Chemical shifts are expressed in δ units (ppm). Microanalytical data were performed by the Microanalytical Data Unit at Cairo University.

2-Cyanomethyl-5-benzylidene-2-thiazolin-4-one (**3**)

To solution of malononitrile (0.01 mole) in acetic acid (100 ml), α-mercaptocinnamic acid (0.01 mole) was added. The reaction mixture was heated under reflux condition for 3 h and then evaporated *in vacuo*. The residue was triturated with ethanol and the resulting product was crystallised from the proper solvent (*cf.* Table I).

2,2'-Bis-(5-benzylidene-4-oxo-2-thiazolin-2-yl)-3-phenylpentane-dinitrile (**5**)

A solution of **3** (0.02 mole) in ethanol (30 ml) was treated with piperidine (1 ml) and benzaldehyde (0.01 mole). The reaction mixture was refluxed for 2 h and then evaporated under reduced pressure. The residue was triturated with water and the resulting solid product filtered off and crystallised from the proper solvent (*cf.* Table I).

5-Benzylidene-2-ethoxycarbonylmethyl-2-thiazolin-4-one (**6**)

A solution of 1 (0.01 mole) in ethanol (30 ml) was treated with ethyl cyanoacetate (0.01 mole) and piperidine (0.1 ml). The reaction mixture was refluxed for three hours and then evaporated under reduced pressure. The remaining solid product was collected by filtration and crystallised from the proper solvent (*cf.* Table I).

Table I. List of compounds **3**, **5**, **6**, **9**, **11**, **14**, **15**, **18** and **19**.

Compound (colour)	Cryst. solvent	M.p. [°C]	Yield [%]	Mol. formula (Mol. weight)	Analysis [%] Found (Required) C	H	N
3 (yellow)	Ethanol	202	60	$C_{12}H_8N_2OS$ (228)	63.0 (63.2	3.8 3.5	12.4 12.3)
5 (yellow)	DMF	272–274	90	$C_{31}H_{20}N_4O_2S_2$ (544)	68.8 (68.4	4.1 3.8	10.0 10.3)
6 (yellow)	Benzene	244–246	40	$C_{14}H_{13}NO_3S$ (275)	60.8 (61.1	4.9 4.7	5.0 5.1)
9 (yellow)	Dioxan	250–252	45	$C_{19}H_{14}N_2O_2S$ (334)	68.2 (68.3	4.1 4.2	8.2 8.4)
11 (yellow)	Ethanol	218	36	$C_{19}H_{12}N_2OS$ (316)	72.5 (72.2	4.0 3.8	8.6 8.9)
14 (colourless)	EtOH/DMF	255	66	$C_{11}H_{10}N_2O_2S$ (234)	56.1 (56.4	4.0 4.3	12.3 12.0)
15 (colourless)	Ethanol	123	56	$C_{28}H_{20}N_4O_2S$ (476)	70.5 (70.6	4.0 4.2	11.6 11.8)
18 (orange)	Dioxan	235	60	$C_{30}H_{25}N_3O_4S$ (523)	68.5 (68.8	4.6 4.8	8.3 8.0)
19 (colourless)	Ethanol	281	60	$C_{25}H_{18}N_2O_2S$ (410)	73.5 (73.2	4.7 4.5	7.0 6.8)

Table II. IR and ^{1}H NMR of compounds listed in Table I.

Compound	IR [cm^{-1}] (selected bands)	^{1}H NMR δ [ppm]
3	3200 (NH), 2220 (CN), 1720 (ring CO) and 1610 (C=C and δ NH)	
5	3350 (NH), 2220 (CN), 1710–1690 (two ring CO) and 1610 (C=C and δ NH)	
6	1725–1690 (ester and ring CO) and 1610 (C=C)	
9	3400 (OH), 2200 (CN), 1710 (CO) and 1610 (C=C)	1.9 (s, 1H, CH), 4.8 (s, 1H, CH), 6.8 (br, s, 1H, OH), 7.3–7.7 (m, 10H, $2C_6H_5$) and 7.9 (s, 1H, CH)
11	2220, 2210 (two CN), 1710 (ring CO) and 1620 (C=C)	4.8 (s, 1H, H-2 thiophen), 7.3–7.8 (m, 10H, $2C_6H_5$) and 7.9 (s, 1H, CH)
14	3250 (NH), 1710 (amide CO) and 1680 (ring CO)	4.2 (s, 2H, CH_2), 5.4 (s, 2H, CH_2), 7.1–7.8 (m, 5H, C_6H_5) and 11.2 (br, s, 1H, NH)
15	3480–3250 (NH_2 and NH), 2220 (CN), 1715 (amide CO), 1680 (ring CO) and 1610 (δ NH_2 and C=C)	4.4 (s, 1H, CH), 5.2 (br, s, 2H, NH_2), 7.2–7.7 (m, 16H, $2C_6H_5$ and C_6H_5CH) and 8.2 (s, 1H, NH)
18	3480–3400 (NH_2 and NH), 1710–1690 (amide, ester and ring CO) and 1610 (δ NH_2 and C=C)	1.5 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 4.8 (s, 1H, CH), 5.4 (br, s, 2H, NH_2), 7.0–7.8 (m, 16H, $2C_6H_5$ and C_6H_5CH) and 11.2 (br, s, 1H, NH)
19	3300 (NH), 1710 (amide CO), 1690 (ring CO) and 1610 (C=C)	7.2–7.8 (m, 17H, C_6H_5 and $2C_6H_5CH$) and 8.2 (s, 1H, NH)

4-Amino-2-benzylidene-5,7-disubstituted-6-phenyl-3-oxo-2,3-dihydro-6H-thiazolo[2,3-a]pyridines (**4** *and* **7**)

A solution of **3** or **6** (0.1 mole) in ethanol (30 ml) was treated with benzylidenemalononitrile (0.1 mole) and piperidine (1 ml). The reaction mixture was heated under reflux condition for 3 h and then evaporated under reduced pressure. The residue was triturated with water and the resulting product filtered off and crystallised from the proper solvent. Compounds **4** and **7** were found to be identical (m.p. and mixed m.p.) with an authentic specimen prepared according to the procedure described by Elnagdi *et al.* [7].

Reaction of **1** *with benzylidenemalononitrile* (**9**)

A solution of equimolecular amounts of **1** and benzylidenemalononitrile (0.01 mole) in ethanol (30 ml) was treated with piperidine (0.2 ml). The reaction mixture was refluxed for 5 h and then evaporated *in vacuo*. The remaining solid product was filtered off and crystallised from the proper solvent (*cf.* Table I).

5-Benzylidene-3,3-dicyano-2-phenyl-4-oxotetrahydrothiophen (**11**)

A suspension of **1** (0.01 mole) in acetic acid (30 ml) was treated with benzylidenemalononitrile (0.01 mole). The reaction mixture was refluxed for 5 h and then evaporated under reduced pressure. The remaining solid product was collected by filtration and crystallised from the proper solvent (*cf.* Table I).

2-Carboxamidomethyl-2-thiazolin-4-one (**14**)

A solution of cyanoacetanilide (0.01 mole) in pyridine (30 ml) was treated with thioglycollic acid (0.01 mole) and the reaction mixture was refluxed for 5 h. The solvent was evaporated under reduced pressure. The remaining solid product was washed with ethanol, filtered off and crystallised from the proper solvent (*cf.* Table I).

4-Amino-2-benzylidene-7-carboxamido-6-phenyl-3-oxo-2,3-dihydro-5-substituted-6H-thiozolo[2,3-a]-pyridines (**15** *and* **18**)

A solution of **14** (0.01 mole) in Me_2SO (50 ml) was treated with benzylidenemalononitrile or benzylidene ethyl cyanoacetate (0.01 mole). The reaction mixture was heated under reflux for 5 h and evaporated *in vacuo*. The residue was triturated with water, the resulting solid product so formed was filtered off and crystallised from the proper solvent (*cf.* Table I).

2-(2-Benzylidene-4-oxo-2-thiazolin-2-yl)-cinnamoanilide (**19**)

A solution of **14** (0.01 mole) in pyridine (30 ml) was treated with benzoylacetonitrile (0.01 mole). The reaction mixture was refluxed for 5 h and then evaporated *in vacuo*. The remaining product was triturated with water, filtered off and crystallised from the proper solvent (*cf.* Table I).

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