Nitriles in Heterocyclic Synthesis: A Route for Synthesis of Functionally Substituted Thiazinones

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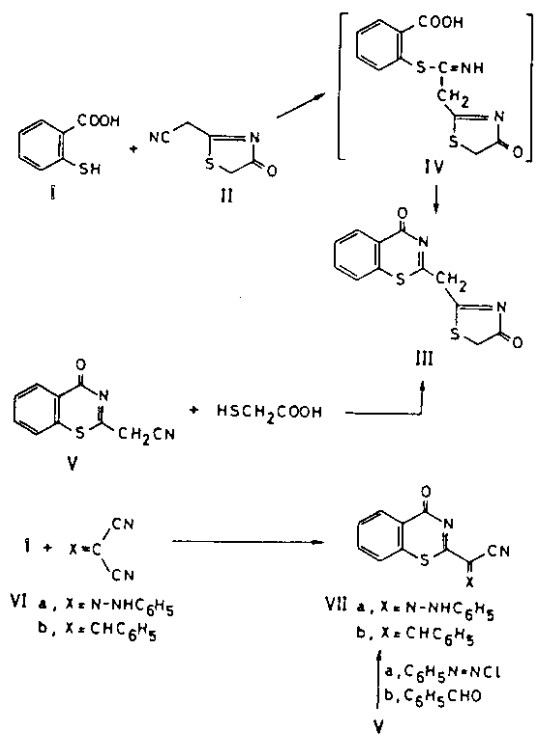
Summary: The reaction of thiosalicylic acid with a variety of activated nitriles is described. Several new benzo [e]-1,3-thiazinones are reported.

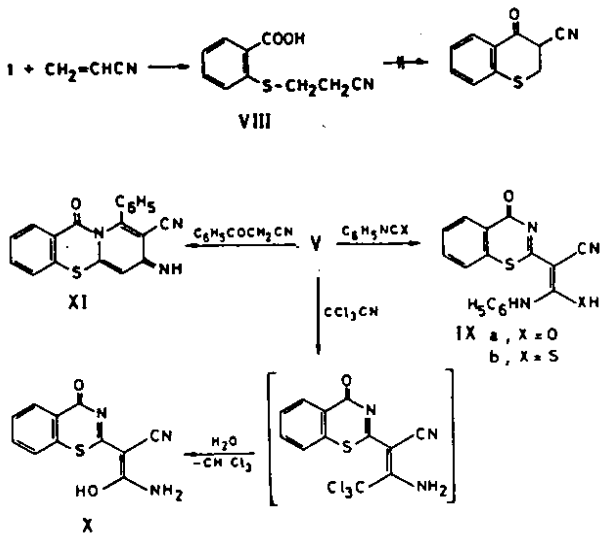
As a part of our program aiming to develop new procedures for synthesis of azoles and azines utilising simple inexpensive starting materials, we have recently reported a novel synthesis of 2-thiazin-4-ones via reaction of thiosalicyclic acid (I) with malononitrile and with ethylcyanoacetate [1]. Now, in order to define the scope and limitation of this approach for thiazin-4-one synthesis, the behaviour of activated nitriles towards (I) was investigated.

Thus, it has been found that (I) reacts with 2-cyanomethyl-2-thiazolin-4-one (II) recently prepared by Elnagdi et al. [2] to yield a product of molecular formula $C_{12}H_8N_2O_2S_2$. The IR spectrum of product revealed the absence of CN absorption. The thiazine structure (III) was established for the reaction product by its synthesis via the reaction of 2-cyanomethylbenzo [e]-1,3-thiazine-4-one (V) with thioglycollic acid. Compound (III) was assumed to be formed through the intermediate (IV).

Similar to the behaviour of (I) with (II), the malononitrile derivatives (VIa,b) reacted with (I) to yield the thiazinones (VIIa,b), the structures of which were established also via synthesis of the reaction products from the reaction of (V) with benzene diazonium chloride and with benzaldehyde respectively.



The reaction of (I) with acrylonitrile under our experimental conditions was also investigated. Similar to previous literature [3], the reaction afforded the cyanoethylated product (VIII). Attempted cyclization of (VIII) under a variety of conditions failed to afford the desired product.



The thiazinone derivatives (IXa,b), and (X) were prepared via reaction of (V) with phenylisocyanate, phenylisothiocyanate, and with trichloroacetonitrile as trials of direct synthesis of these derivatives from the reaction of (I) with the appropriate activated nitrile failed to afford the desired products.

Fusion of (V) with benzoylacetonitrile at 160°C for 1 hour yielded 2-cyano-3-imino-1-phenylpyrido [2,1-b] benzthiazin-10-one (XI).

Experimental

All melting points are uncorrected. IR spectra were recorded on a Beckman spectrophotometer, ^{1}H NMR on Varian EM-390-90 MHz spectrometer. The microanalyses were performed by the microanalytical unit at Cairo University.

Reaction of active nitriles with thiosalicylic acid (General procedure)

Thiosalicyclic acid (0.01 mole) was refluxed with 0.01 mole of the appropriate nitrile (II; VIa, b; and acrylonitrile) in 20 ml of pyridine for 2 hours. The reaction mixture was triturated with ice-cold water and the solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. table 1).

Reactions of 2-cyanomethylbenzo [e] 1,3-thiazin-4-one (V) with:
a) Thioglycollic acid

Equimolecular amounts of compound (V) (0.01 mole) and thioglycollic acid (0.01 mole) were refluxed in 20 ml pyridine for 2 hours. The reaction mixture was poured on ice-cold water and the resulting solid product (2g, 72%) was identified as compound (III) (m.p. and mixed m.p) 252°C.

b) Benzenediazonium chloride

An ice-cold solution of diazotized aniline (0.01 mole) was added to an ethanolic solution of (V) (0.01 mole) in the presence of sodium acetate (0.01 mole). The solid product so formed, was collected by filtration, washed with water and crystallized from the proper solvent as compound (VIIa) (m.p. and mixed m.p) 222°C, yield 71%.

c) Benzaldehyde

Benzaldehyde (0.01 mole) was heated with (V) at 160°C (bath T) for 1 hour the product, so formed, was collected and crystallized from the proper solvent as compound (VIIb) (m.p. and mixed m.p.) 245°C; yield 62%.

d) Phenylisocyanate and phenyl isothiocyanate

Compound (V) (0.01 mole) was heated with either phenylisocyanate (0.01 mole) or phenylisothiocyanate (0.01 mole) at 160°C (bath T) for 1

Table-1

Compound	Solvent	M.P. (°C)	Yield (%)	Mol.Formula (mol.wt.)	Analysis Found/Calcd. C%	H%	N%
(III)	Acetic acid	252	65	$C_{12}H_8N_2O_2S_2$ 276	52.5 52.17	2.60 2.89	10.50 10.14
(VIIa)	Ethanol	222	70	$C_{16}H_{10}N_4OS$ 306	62.50 62.74	3.00 3.26	18.50 18.30
(VIIb)	Acetic acid	245	60	$C_{17}H_{10}N_2OS$ 290	70.60 70.34	3.10 3.44	9.90 9.65
(VIII)	Ethanol	180	80	$C_{10}H_9NO_2S$ 207	58.30 57.97	4.20 4.34	6.80 6.76
(IXa)	Acetic acid	250	70	$C_{17}H_{11}N_3O_2S$ 321	63.80 63.55	3.20 3.42	13.30 13.08
(IXb)	Ethanol	260	75	$C_{17}H_{11}N_3OS_2$ 337	60.10 60.53	3.00 3.26	12.50 12.46
(X)	Ethanol	230	60	$C_{11}H_7N_3O_2S$ 245	53.80 53.87	2.40 2.85	17.00 17.14
(XI)	Acetic acetic	225	70	$C_{19}H_{11}N_3OS$ 329	69.00 69.30	3.50 3.34	12.80 12.76

hour. The solid product, so formed, was crystallized from the proper solvent (cf. Table 1).

e) Trichloroacetonitrile

Compound V (0.01 mole) was refluxed with trichloroacetonitrile (0.01 mole) in toluene (30 ml) in the presence of 0.1 ml of triethylamine for 3 hours. The reaction mixture was poured on ice-cold water. The solid product was collected by filtration and crystallized from the proper solvent (cf. Table 1).

f) Benzoylacetonitrile

Compound (V) (0.01 mole) was heated with benzoylacetonitrile (0.01 mole) at 160°C (bath T) for 1 hour. The solid product, so formed, was crystallized from the proper solvent (cf. Table 1).

Table-2

Compd.	IR. cm^{-1}	^1H NMR. ppm.
(III)	1730,1690 (two ring C=O); 1640, 1600 (two C=N).	3.25(q, 2H,CH_2); 4.15 (q,2H,CH_2); 7.3-7.8 (m,4H,aromatic protons).
(VIIa)	3200(NH);2200(CN);1680(ring C=O); 1640 (C=N).	7.2-8.0(m,9H,aromatic protons); 8.25 (d,1H,NH).
(VIIb)	2190(CN);1700(ring C=O); 1660 (C=N).	
(VIII)	2220(CN); 1700 (acid C=O).	2.9(t,2H,CH_2); 3.25(t,2H,CH_2); 4.8 (s,br, 1H,CO_2H); 7.16-7.9(m,4H,aromatic protons).
(IXa)	3360(NH);2210(CN);1720 (exocyclic C=O);1690(ring C=O); 1640 (C=N).	3.45(s,1H,CH);7.5-7.8(m,9H,aromatic protons) 8.45(s,br,1H,NH).
(IXb)	3330(NH);2200(CN); 1690 (ring C=O);1650(C=N); 1550 (C=S).	
(X)	3600(OH); 3320(NH_2);2200(CN); 1690(ring C=O);1640(C=N).	
(XI)	3350(br.NH);2200(CN) and 1690 (CO)	7.9(m,9,phenyl protons+methine proton +3 phenylene proton); 8.5(m, 2, NH+the phenylene proton near the carbonyl group).

References

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3. H.A. Bruson, "Cyanoethylation in Organic Reactions", Ed. by R.Adams, Academic Press, New York, 1952, V, 79.