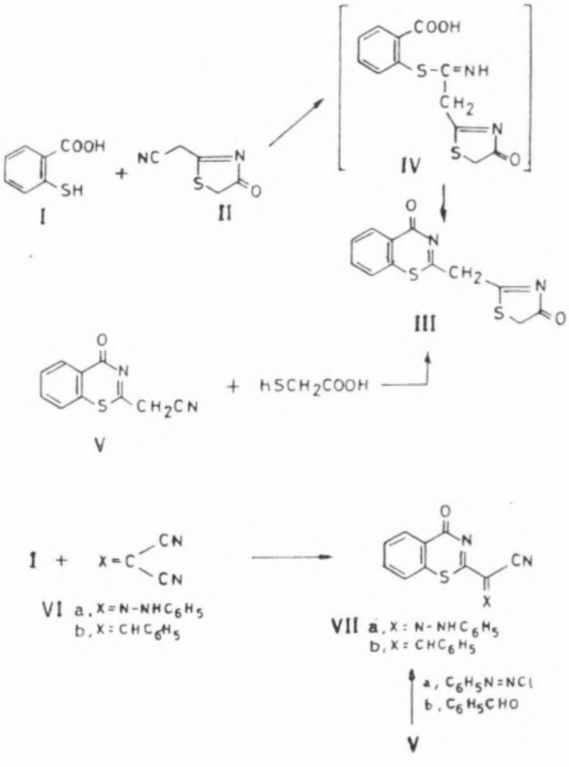
NOSRAT M. ABED
NADIA S. IBRAHIM
SUZAN I. AZIZ
Chemistry Department,
Faculty of Science,
Cairo University,
Giza, A. R. Egypt.

NITRILES IN HETEROCYCLIC SYNTHESIS: A ROUTE FOR SYNTHESIS OF FUNCTIONALLY SUBSTITUTED THIAZINONES

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 thiosalicylic acid [1] 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 a variety of activated nitriles toward 1 was investigated.

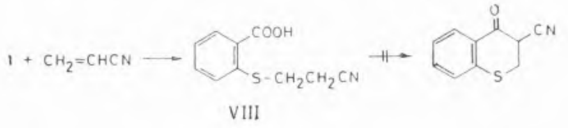


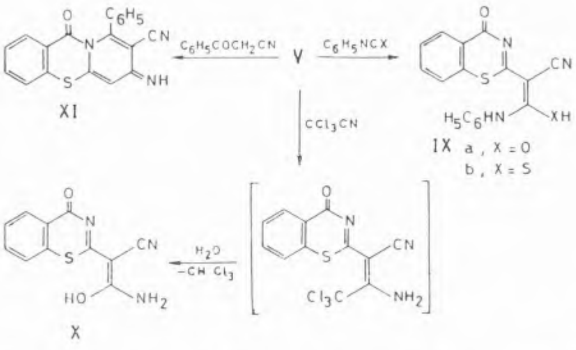
Thus, it has been found that I reacts with 2-cyanomethyl-2-thiazolin-4-one (II) recently prepared by Elnagdi et al. [2] to yield a product of molecular formula $C_{12}H_8N_2O_2S_2$. The IR spectrum of the product revealed the absence of CN absorption. The thiazine structure III was established for the 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 VII,a,b. The structure of which was 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 on V with benzoylacetonitrile at 160°C for 1 h. yielded 2-cyano-3imino-1-phenylpyrido [2,1-b] benzthiazin-10-one XI.

Experimental Section:

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): Thiosalicylic acid (0.01 mol) was refluxed with 0.01 mol of the appropriate nitrile (II; VIa,b; and acrylonitrile) in 20 cm^3 of pyridine for 2 h. 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) *Thioglycollicacid :*

Equimolecular amounts of compound V (0.01 mol) and thioglycollic acid (0.01 mol) were refluxed in 20 cm^3 pyridine for 2 h. The reaction mixture was poured on ice-cold water and the resulting solid product (2 g, 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 mol) was added to an ethanolic solution of V (0.01 mol) in the presence of sodium acetate (0.01 mol). 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 72 %.

c) *Benzaldehyde :*

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

d) *Phenylisocyanate and phenyl isothiocyanate :*

Compound V (0.01 mol) was heated with either phenylisocyanate (0.01 mol) or pheny-

Table 1

Compound	Solvent	M.P./°C	Yield (%)	Mol. Formula (mol. wt.)	Analysis Formed/(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)
VII a	Ethanol	222	70	$C_{16}H_{10}N_4OS$ 306	62.56 (62.74)	3.00 (3.26)	18.50 (18.30)
VII b	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)
IX a	Acetic acid	250	70	$C_{17}H_{11}N_3O_2S$ 321	63.80 (63.55)	3.20 (3.42)	13.30 (13.08)
IX b	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 acid	225	70	$C_{19}H_{11}N_3OS$ 329	69.00 (69.30)	3.50 (3.34)	12.80 (12.76)

Table 2

Compound	IR/cm^{-1}	^{1}H 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).
VII a	3200 (NH); 2200 (CN); 1680 (ring C=O); 1640 (C=N).	7.2 -8O (m, 9H, aromatic protons); 8.25 (d, 1H, NH).
VII b	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).
IX a	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).
IX b	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 of phenylene proton); 8.5 (m, 2, NH + the phenylene proton near the carbonyl group).

lisothiocyanate (0.01 mol) at 160°C (bath T) for 1 h. The solid product, so formed, was crystallized from the proper solvent (cf. Table 1).

e) *Trichloroacetonitrile :*

Compound V (0.01 mol) was refluxed with trichloro-acetonitrile (0.01 mol) in toluene (30 cm^3) in the presence of 0.1 cm^3 of triethylamine for 3 h. 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 mol) was heated with benzoylacetonitrile (0.01 mol) at 160°C (bath T) for 1 h. The solid product. so formed, was crystallized from the proper solvent (cf. Table 1).

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RESUMO

«Nitrilos em síntese heterocíclica: uma via para a síntese de tiazinonas funcionalmente substituídas.»

Descrevem-se as reações do ácido tiosalicílico com uma série de nitrilos activados. Descrevem-se pela primeira vez várias benzo[e]-1,3-tiazinonas.