NITRILES IN HETEROCYCLIC SYNTHESIS: A NEW APPROACH FOR THE SYNTHESIS OF THIAZINONES

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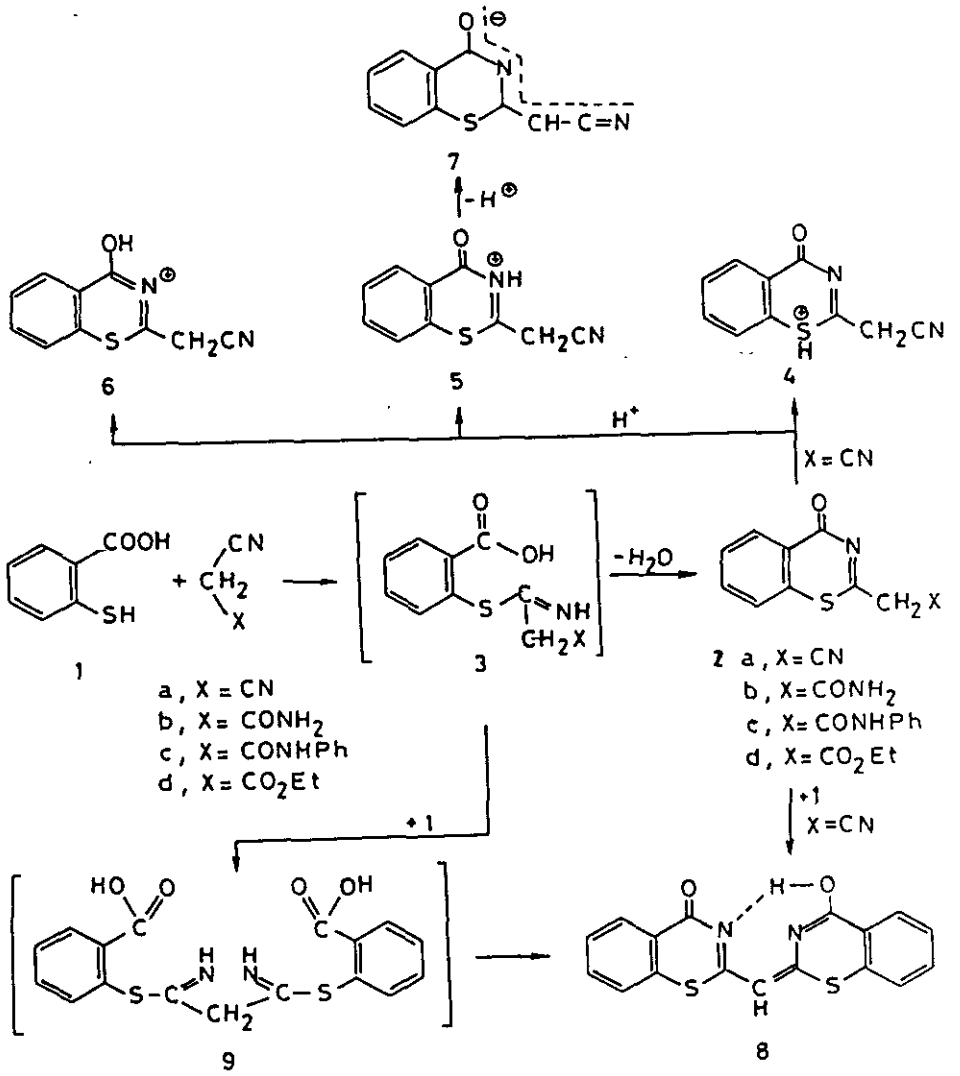
Abstract - Synthesis of thiazines via the reaction of thiosalicylic acid with malononitrile, ethyl cyanoacetate and other polyfunctional nitriles is reported.

Polyfunctional nitriles are highly reactive compounds that have been extensively utilized in organic synthesis.[1,2] In the last decade, we have been involved in a program aiming to explore the potential scope and limitation of the utility of polyfunctional nitriles in heterocyclic synthesis.[3] During this phase of our research, we have developed a new synthesis of 2-thiazolin-4-ones from reaction of cyanocarbonic acid derivatives with thioglycolic acid.[4-7] We have been particularly interested to see if the reaction of polyfunctional nitriles with bidentate thioles reagents can be utilized as a general approach for synthesis of sulphur containing heterocycles.

In the present paper, we report the result of our investigation on the reaction of thiosalicylic acid (1) with cyanocarbonic acid derivatives. Thus it has been found that when equimolecular amounts of malononitrile (0.01 mole) and 1 (0.01 mole) were refluxed in acetic acid (50 ml) for 2 h, a mixture of two products of melting points 220°C and 310°C in the ratio of 3:1 respectively was obtained. These were separated by fractional crystallization from ethanol. The product of mp 220°C revealed a molecular formula of $C_{10}H_6N_2OS$. The thiazine structure 2a was assigned for this product based on IR and ^1H NMR data. Thus, the ^1H NMR in trifluoroacetic acid (TFA) revealed low field aromatic proton at δ 8.22 for H-5 proton, a multiplet for three protons extending from δ 7.25 - 7.9 ppm for H-6, H-7 and H-8. The methylene protons appeared as multiplet at δ 4.69 - 5 ppm indicating that this molecule exists in TFA as a mixture for 2a and its protonated forms 4-6. A signal for 0.50 H appeared at δ 6.66 ppm for the protonated form. However, it is difficult to decide if protonation afforded, 4, 5 or 6, most likely the three forms exist.



In order to shed further light on the actual structure of this reaction product, its pKa was determined spectrophotometrically and a value of 8.5 was observed. This indicates that the molecule is more acidic than phenolate anion. This extra acidity may be rationalized by assuming that the conjugate base of this molecule is stabilized by the resonance of negative charge on the oxygen, nitrogen, ring carbons and the exocyclic CH-CN moiety (cf. structure 7).

The product which exhibit high melting point could be formed on treatment of 2a with another molecule of 1 and was assigned structure 8 based on its analytical data. Compound 2a could be obtained as the sole reaction product on treatment of

1 with malononitrile in refluxing pyridine. However, under acidic conditions compound 8 was always obtained as a byproduct with 2a. It seems that the reaction of 2a with 1 in acidic medium proceeds at an appreciable rate so that this reaction competes successfully leading to the formation of 8. However the possibility, that 1 reacts with malononitrile to yield acyclic intermediate 3 which then either loose a water molecule to yield 2a or reacts further with 1 to yield 9 which affords final isolable 8, cannot be overlooked.

Similar to the behaviour of 1 toward malononitrile, it reacted with cyanoacetamide and cyanoacetanilide in refluxing pyridine to yield the corresponding thiazines 2b,c.

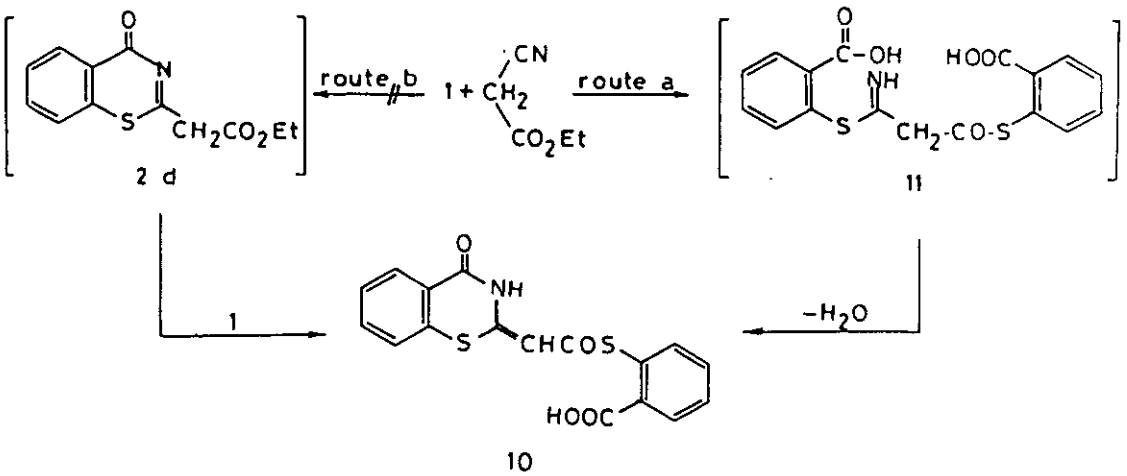
In contrast to the observed reaction of 1 with malononitrile and cyanoacetamides, ethyl cyanoacetate (0.01 mole reacted with 1 (0.01 mole) when refluxed in ethanol (50 ml) in presence of 0.1 ml of triethylamine for 4 h yielding a product of molecular formula $C_{17}H_{11}NO_4S_2$. Attempts to effect this reaction in acetic acid were unsuccessful. Structure 10 was suggested for the product based on spectral data. Thus, ^1H NMR of the reaction product indicated that the compound exists mainly in the tautomer shown in formula as it revealed absence of any absorption for protons linked to sp^3 carbons.

When 1 was treated with ethyl cyanoacetate in refluxing pyridine for 3 h, compound 2d was formed. Attempts to convert 2d into 10 on treatment with 1 (route b) in ethanolic triethylamine were unsuccessful. The thiazine derivative 2d was recovered unchanged indicating that 10 was formed via route a.

Cyanothioacetamide (0.01 mole) reacted with 1 (0.01 mole) in refluxing pyridine (30 ml) for 3 h to yield the bithiazine derivative 12. This is assumed to be formed via self condensation of intermediate thiazine to yield the isolable product. Similar condensation of active methylene reagents with thioamides are well known.[10]

Trichloroacetonitrile (0.01 mole) was refluxed with 1 (0.01 mole) in dry toluene (30 ml) for 3 h to yield a product of molecular formula $C_{16}H_8NO_2S_2Cl_3$. This was assigned structure 13 based on analytical and spectral data. Similar observation has been very recently reported by one of us[11] for the reaction of methyl salicylate with trichloroacetonitrile.

All the reported products were formed in good yields. The chemistry of these compounds is now under investigation.


route b
route a
1 +
2 d
11
1
-H2O
10

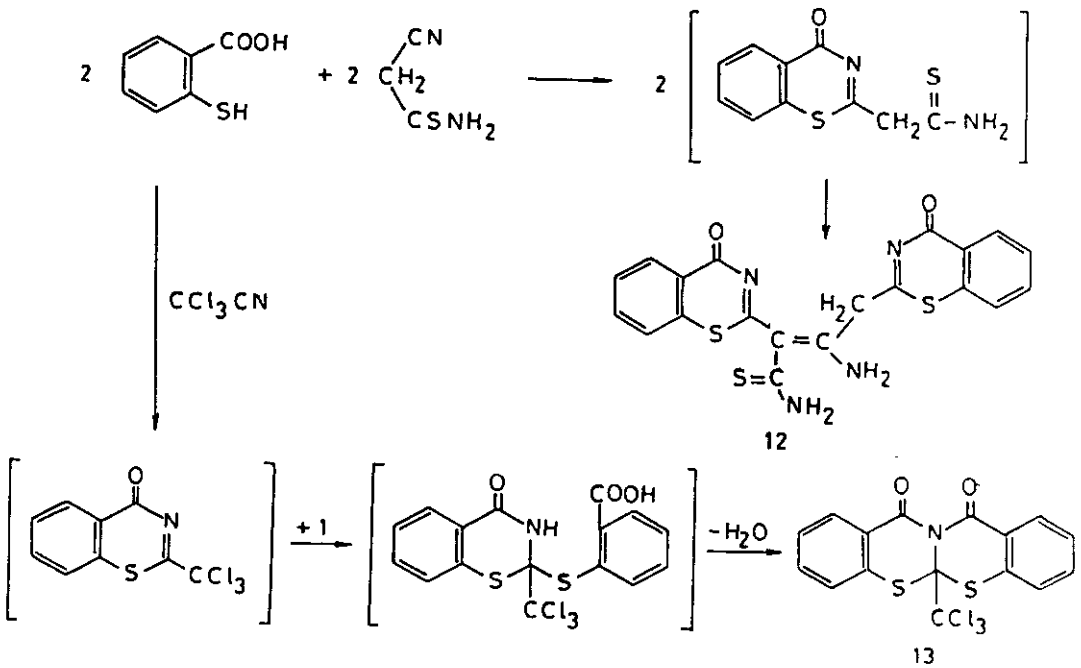

2
+ 2
CCl3CN
12
+ 1
-H2O
13

Table 1: List of compounds 2a, 2b, 2c, 2d, 8, 10, 12, 13,

Compound*	Solvent of crystallization	Colour	Mp. (°C)	Yield (%)	Mol. formula
2a	ethanol	yellow	220	60	$C_{10}H_6N_2OS$
2b	D M F	colourless	295	75	$C_{10}H_8N_2O_2S$
2c	acetic acid	yellow	236	65	$C_{16}H_{12}N_2O_2S$
2d	ethanol	yellow	145	90	$C_{12}H_{11}NO_3S$
8	ethanol	yellow	310	20	$C_{17}H_{10}N_2O_2S_2$
10	ethanol	colourless	300	65	$C_{17}H_{11}NO_4S_2$
12	ethanol	red	292	70	$C_{20}H_{14}N_4O_2S_3$
13	toluene	yellow	175	80	$C_{16}H_8NO_2S_2Cl_3$

* Satisfactory elemental analyses for all the newly synthesized compounds were obtained.

Table 2: IR and ^{1}H NMR data of compounds 2a, 2b, 2c, 2d, 8, 10, 12, 13.

Compound	IR, cm^{-1}	^{1}H NMR δ ppm
2a	3020 (aromatic C-H); 2990, 2900, 2870 (CH_2); 2200(C≡N) and 1710, 1670 (amide I and II bands)	4.69-5(m,methylene protons), 7.25-8.22(m, aromatic protons).
2b	3420(amide. NH_2);1700,1680(C=O)and 1640(C=N).	4.6(q,2H,CH_2);7.2-8.2(m, 4H,aromatic protons),9.2 (s,br,2H,NH_2)
2c	3420(amide NH); 1690,1660 (C=O)and 1640(C=N).	4.6(q,2H,CH_2);7.4-8.2(m, 9H,aromatic protons);9.2 (s,br,1H,NH).
2d	3080,2980(saturated CH_2);1700(ester C=O);1680(ring C=O)and 1640(C=N).	1.38(t,3H,CH_3);3.5(q,2H, CH_2);4.2(q,2H,ester CH_2); 7.6-8.0(m,4H,aromatic protons)
8	3300,2400(OH dimer)and 1700,1650 (ring C=O)	
10	3500,2300(OH dimer and CH)and 1750, 1650(C=O group)	6.83-8.22(m,10H,aromatic protons,NH and OH).

12	3450,3390(NH_2);3080,2990(saturated CH_2); 1690,1680(two ring CO); 1640(C=N) and 1630(C=C).	3.6(q,2H,CH_2);7.2-8.2(m, 8H,aromatic protons);9.6-10.2(m,br,4H,two NH_2).
13	1690 (two ring C=O)	

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