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Cinnamonitriles in Heterocycles Synthesis: Reaction of α,β-Unsaturated Nitriles with Thioglycolic Acid

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Abstract □ 7H-thiazolo-[3,2-a]-pyridines as potential antimicrobial agents were prepared by reaction of α,β-unsaturated nitriles and thioglycolic acid.

Keywords □Cinnamonitriles, thioglycolic acid, 7H-thiazolo-[3,2-a]-pyridines, bacterial activity

Cinnamonitriles are highly reactive reagents that have been extensively utilized in heterocyclic synthesis.[1-4] Also, the considerable biological and pharmacological activity of the fused thiazoles[5-7] led us to study the synthesis and the various changes in the structures of these compounds, aiming to synthesize less toxic and more potent drugs having better properties than the one already marketed.

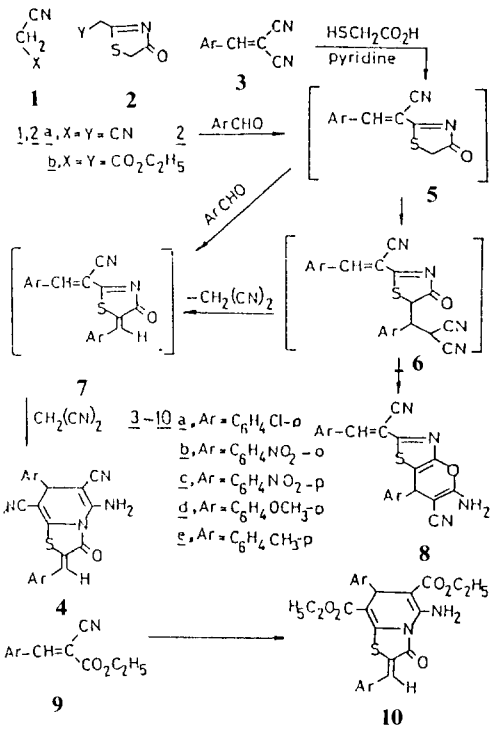
Thus, it has been found that **3a** react with thioglycolic acid to yield a crystalline product of molecular formula $C_{22}H_{12}N_4OSCl_2$ (M^+ 451). This was assumed to be the thiazolo-[3,2-a]-pyridine **4a** or the pyrano-[2,3-d]-thiazole **8a**. However, the possibility that the reaction product is the pyranothiazole **8a** resulting from cyclization of **6** was elemented based on the IR spectrum of the isolated product which revealed, a band at 1670-1800 cm^{-1} for ring carbonyl group. This band is not expected in IR spectrum of **8**, however it must be expected in IR spectrum of **4**. The formation of **4a** from reaction of **3a** with thioglycolic acid is assumed to proceed *via* intermediacy of **5a** formed by addition of thioglycolic acid to one of the cyano functions in **3a**. Compound **5a**, so formed, further react with one molecule of **3a** to yield the Michael adduct intermediate **6**. This then lose malononitrile to yield the diarylidene compound **7a** which react with the elemented malononitrile to yield the final isolable 7H-thiazolo-[3,2-a]-pyridine **4a**. In a manner similar to the behaviour of **3a** toward thioglycolic acid, **3b-e** were reacted with thioglycolic acid to give the corresponding **4b-e**.

In order to provide evidance for the proposed reaction route, the arylidenes **5a-e** were prepared *via* interaction of **2a** and the appropriate aldehydes in ethanolic triethylamine. Compounds **5a-e** were converted into the corresponding **7a-e**. Treating **7a-e** with malononitrile affords **4a-e**.

On the same bases, heating of thioglycolic acid with aryldicyanoacetate **9a-e** in refluxing pyridine afforded the corresponding 7H-thiazolo-[3,2-a]-pyridines **10a-e**. Structure **10** was confirmed *via* the IR and ^{1}H-NMR data of the isolated products which are in good agreement with structure **10**.

BACTERIOLOGICAL TESTING AND RESULTS

Four bacterial cultures selected at random for initial screening included both gram positive bacteria (*Bacillus subtilis, staphylococcus aureus*) and gram negative bacteria (*Pseudomonas auregenosa, Echerichia coli*) of several genra having different nutritional requirements and metabolic activities. Several new compounds were tested *in vitro* at concentration 100 μg/ml. Data pertaining to the relation between structures and bacterial activity of the newly synthesized compounds are presented in Table I. It is to be noted first that most of listed compounds have marked activity against *Pseudomonas aure-*



genosa. Also, it has been found that compounds **7a**, **7b** and **7c** show the greatest antimicrobial activity. However, compounds **10c**, **10d** and **10e** show the less antimicrobial activity.

EXPERIMENTAL METHODS

All melting points are uncorrected. IR spectra were recorded in KBr disc on ashimadzu 408 spectrophotometer. ^{1}H-NMR spectra were measured in DMSO on Varian EM-390 NMR spectrometer (90 MHz), using TMS an internal standard and chemical shifts are expressed as δ ppm. Microanalysis were performed by the microanalytical unit at Cairo University.

Reaction of 3a-e and 9a-e with thioglycolic acid: General procedure

A solution of **3a-e** or **9a-e** (0.02 mol) and thioglycolic acid (0.01 mol) in pyridine (50 ml) was heated under reflux for three hours. The solvent was then evaporated under reduced pressure and the remaining solid product was collected and crystallized

Table I. Antimicrobial activity of compounds 4, 5, 7 and 10 against bacteria strains

Compd. in conc. 100 μg/ml	Inhibition zone (cm^2)			
	Gram postive		Gram negative	
	Bacillus subtilis	*Staphyloco-cuss aureus*	*Echricia coli*	*Pseudomonas auregenosa*
4a	++	++	++	++
b	+	+	+	+++
c	+	+	+	+++
d	−	−	+	+
d	+	+	+	+
e	−	+	+	−
5a	++	++	++	++
b	−	−	+	+
c	+	+	+	++
d	+	−	+	+
7a	+++	++	+++	+++
b	++	++	++	+++
c	−	−	−	++
e	+	+	+	+++
10a	+	+	++	+
b	+	+	−	+
c	−	−	−	−
e	+	−	−	+

−: 1 cm^2; +: 1-1.5 cm^2; ++: 1.5-2 cm^2; +++: 2 cm^2

Table II. Analytical data of the synthesized compounds

Compound	mp/℃	C.S.	Formula	Calc./found			
			(mol.wt)	C %	H %	N %	S %
4a	242	E/D	$C_{22}H_{12}Cl_2N_4OS$	58.59	2.7	12.4	7.1
	(85)		(451)	58.9	2.9	12.1	7.5
b	300	D	$C_{22}H_{12}N_6O_3S$	55.9	2.5	17.8	6.8
	(90)		(472)	55.7	2.8	17.5	6.7
c	300	D	$C_{22}H_{12}N_6O_3S$	55.9	2.5	17.8	6.8
	(92)		(472)	56.33	2.3	18.1	6.9
d	272	d	$C_{24}H_{18}N_4O_3S$	65.1	4.1	12.7	7.2
	(82)		(442)	65.3	4.3	12.3	7.7
e	225	A	$C_{24}H_{18}N_4OS$	70.22	4.4	13.7	7.8
	(85)		(410)	70.4	4.7	13.4	7.5
5a	151	E	$C_{12}H_7ClN_4O_2OS$	54.9	2.7	10.7	12.2
	(65)		(262.5)	54.6	3.1	11.1	12.3
b	178	E	$C_{12}H_7N_3O_3S$	52.8	2.6	52.4	11.7
	(66)		(273)	52.6	2.5	15.3	11.5
c	210	E	$C_{12}H_7N_3O_3S$	52.8	2.6	15.4	11.7
	(66)		(273)	52.6	2.5	15.4	11.6
d	190	E	$C_{13}H_{10}N_2O_2S$	60.4	3.9	10.8	12.4
	(68)		(258)	60.7	3.5	11.2	12.6
e	162	E	$C_{13}H_{10}N_2OS$	64.5	4.1	11.6	13.2
	(60)		242)	64.7	4.3	11.5	12.9
7a	218	D	$C_{19}H_{10}Cl_2N_2OS$	59.2	2.6	7.3	8.3
	(75)		(406)	56.0	2.7	14.0	7.7
b	255	d	$C_{19}H_{10}N_4O_3S$	56.2	2.5	14.0	7.9
	(80)		(406)	56.0	2.7	14.0	7.7
c	236	d	$C_{19}H_{10}N_4O_3S$	56.2	2.5	13.8	7.9
	(80)		(406)	56.4	2.7	13.7	8.1
d	217	d	$C_{21}H_{16}N_2O_3S$	67.0	4.3	7.4	8.5
	(78)		(376)	67.3	4.5	7.9	8.7
e	195	d	$C_{21}H_{16}N_2OS$	73.3	4.6	8.1	9.3
	(80)		(344)	73.7	4.4	7.9	9.6
10a	221	E	$C_{26}H_{22}Cl_2N_2O_3S$	57.3	4.1	5.1	5.9
	(85)		(545)	57.1	3.8	5.3	6.2
b	275	E	$C_{26}H_{22}N_4O_9S$	55.1	3.9	9.9	5.6
	(80)		(566)	55.4	3.7	10.2	5.4
c	288	A	$C_{26}H_{22}N_4O_9S$	55.1	3.9	9.9	5.6
	(80)		(566)	55.5	4.2	10.2	5.3
d	180	A	$C_{28}H_{28}N_2O_7S$	62.7	5.3	5.2	6.0
	(75)		(536)	63.1	5.1	5.5	6.3
e	202	D	$C_{28}H_{28}N_2O_5S$	66.7	5.6	5.6	6.3
	(80)		(504)	67.0	5.9	5.2	6.6

E=Ethanol; D=Dixane; A=acetic acid; d=D.M.F

from the proper solvent to give the corresponding **4a-e** or **10a-e** (cf. Tables II and III).

Reaction of thiazolenenone 2a with aromatic aldehydes

Formation of 5a-e

Equimolar amounts of **2a** and the appropriate aldehyde (0.01 mol) in ethanol (50 m*l*) was treated with few drops of piperidine. The reaction mixture

Table III. IR and ^{1}H-NMR of the synthesized compounds

Compound	IR (cm $^{-1}$)	^{1}H-NMR (δ ppm)
4a	3430-3350 (NH_2); 2220 (CN) and 1690 (ring CO)	4.5 (s, 1 H, pyridine H-6); 6.7 (br, s, 2H, NH_2) and 7.2-8 (m, 9H, $2C_6H_4$ and ylidene CH)
4b	3450-3350 (NH_2); 2200 (CN), 1690 (ring CO) and 1580 (NO_2)	4.5 (s, 1H, pyridine H-6); 6.75 (br, s, 2H, NH_2) and 7.2-8 (m, 9H, $2C_6H_4$ and ylidene
4d	3460-3350 (NH_2); 2980-2950 (CH and CH_3); and 1690 (ring CO)	3.8-3.9 (two singlets, 6H, $2OCH_3$); 4.8 (s, 1H, pyridine H-6) and 6.7-8.2 (m, 11H, aromatic, ylidene and NH_2 protones)
4e	3450-3350 (NH_2); 2980-2950 (CH and CH_3; 2200 (CN) and 1690 (ring CO)	1.3-1.4 (two singlets, 6H, 2 OCH_3); 4.8 (s, 1H, pyridine H-6) and 6, 7-8 (m, 11H, aromatic, ylidene and NH_2 protones)
5a	2220 (CN); 1700 (ring CO) and 1620 (C=C)	5.6 (s, 1H, thiazole H-5); 7.0-7.8 (m, 5H, aromatic and ylidene protones) and 11.2 (s, 1H, OH)
5d	2220 (CN); 1700 (ring CO), 1620 (C=C) and 2980-2950 (CH_2 and OCH3)	5.8 (s, 1H, thaizole H-5); 7.1-7.8 (m, 5H, aromatic and ylidene protones); /11.2 (s, 1H, OH) and 3.8 (s, 3H, OCH_3)
5e	2220 (CH); 1700 (ring CO), 1620 (C=C) and 2980-2950 (CH_2 and CH_3).	
7a	2220 (CN); 1700 (ring CO), 1610 (C=C)	8.3 (s, 1H, arylidene CH) and 7.9-7.0 (m, 9H, aromatic and arylidene protons).
7b	2210 (CN); 1700 (ring CO); 1610 (C=C) and 1590 (NO_2).	
7d	2210 (CN); 1690 (ring CO); 1610 (C=C) and 1590 (NO_2).	3.8-4.0 (two singlets, 2 OCH_3); 6.9-7.8 (m, 9H, aromatic and arylidene protones) and 8.2 (s, 1H, arylidene proton).
10a	3440, 3350 (NH_2); 3000-2950 (C_2H_5, OCH_3); 2210 (CN) and 1730, 1725, 1690 (ester CO and ring CO).	1.2 (2t, 6H, $2CH_3$); 4.1 (2q, 4H, $2CH_2$); 5.0 (s, 1H, pyridine H-6), 6.2 (br, s, 2H, NH_2) and 7.1-7.9 (m, 9H, aromatic and arylidene protons).
10d	3420, 3380 (NH_2); 3000-2950 (CH_2 and CH_3), 1730 ester CO); 1670 (ring CO) and 1615 (CH=CH)	1.2 (m, 6H, $2CH_3$); 2.9 (s, 6H, 2 OCH_3); 3.5 (br, s, 2H, NH_2), 4.7 (s, 1H, pyridine H-6), 6.7-7.7 (m, 8H, aromatic protons) and 8.3 (s, 1H, arylidene CH).

was refluxed for one hour, the solvent was then removed *in vacuo* and the remaining product collected and crystallized from ethanol to give **5a-e** (cf. Tables II and III).

Synthesis of Diarylidenes 7a-e

Equimolar amounts of **5a-e** and the appropriate aldehyde (0.01 mol) was refluxed in methanolic methoxide [(50 m*l*) methanol containing 0.3g dissolved sodium metal] for three hours. The solvent was then removed *in vacuo* and the remaining product was triturated with water and neutralized with HCl. The solid product, so formed, was collected by filtration and crystallized from the proper solvent to give the corresponding **7a-e**.

Reaction of 7a-e with Malononitrile

Equimolar amounts of **7a-e** and malononitrile (0.01 mol) in pyridine (30 m*l*) was heated under reflux for two hours. The solvent was then removed *in vacuo* and remaining solid product was collected and crystallized from the proper solvent to give the corresponding **4a-e** (cf. Tables II and III).

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