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Cycloaddition Reactions of 5-(2-Thienyl)methylene Derivatives of Thiazolidinone-4-Thiones and Their Antimicrobial Activities

Hamed A. Ead[§], **Nadia H. Metwalli and Nagwa M. Morsi***
*Department of Chemistry, and *Department of Botany,*
Faculty of Science, University of Cairo, Giza, Egypt
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Abstract□The cycloaddition of the newely synthesized 5-(2-thienyl)methylene derivatives of thiazolidinone-4-thiones, **2a-c** to acrylonitrile (**3a**), ethyl acrylate (**3b**), N-phenylmaleimide (**6**) and dimethyl fumarate (**8**) has been evaluated. Under thermal reaction conditions [4 + 2] cycloaddition proceeds with complete site and regioselectivity to yield the cycloadduct, **4, 5, 7** and **9**, respectively. The antimicrobial activities of some of the new products were tested.

Keywords□5-(2-Thienyl)methylene thiazolidinone-4-thiones, cycloaddition, antimicrobial activities

As a part of our studies directed towards the synthesis of new compounds of biological potentialities,[1-3] we report here the results of cycloaddition of some dienophiles with the newely synthesized (2-thienyl)methylene derivatives of 2-thiazolidinone-4-thiones.

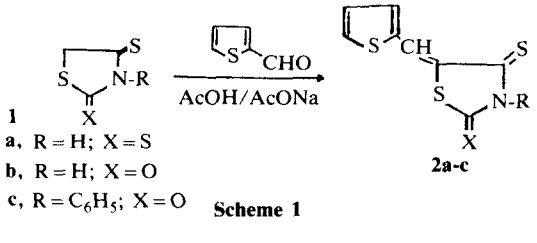
The 5-(2-thienyl)methylene-2-thiazolidinone-4-thiones, **2a-c**, needed for this investigation were prepared by heating equimolar quantities of **1a-c** and thiophene-2-carboxaldehyde in glacial acetic acid in presence of anhydrous sodium acetate (Scheme 1).

When the deeply coloured **2a-c** were refluxed with acrylonitrile (**3a**) or ethyl acrylate (**3b**) in glacial acetic acid, the colourless 6-cyano or 6-carboxy-7-(2-thienyl)-tetrahydrothiopyrano-7H[2,3-d]-thiazole derivatives, **4a-c** and **5a-c** were obtained (Scheme 2). The assigned structure for products, **4** and **5** were established from elemental and spectral data. ^{1}H-NMR spectra (δ ppm) of all compounds reveal one doublet at 4.75 corresponding to H-7 and a two doublets at 2.7 and 3.53 corresponding to H-5ax and H-5eq in addition to multiplet at 3.61-4.0 corresponding to H-6.

Heating of equimolar amounts of **2a-c** and N-phenylmaleimide (**6**) under reflux in glacial acetic acid gave a quantitative yield of the cycloadducts, **7a-c** (Scheme 3). The ^{1}H-NMR spectra (δ ppm) of **7** show two doublets at 5.1 and 5.3 (J = 9Hz) corresponding to H-5 and H-7 respectively, in addition to a two doublets at 4.3-4.1 corresponding to H-6. On the basis of the coupling constant the cycloadducts **7a-c** were assigned the indicated cis-configuration.[4]

The cycloaddition of **2a-c** with dimethyl fumarate in refluxing glacial acetic acid gave the thiazolo-thiopyrano cycloadducts, **9a-c**. The ^{1}H-NMR spectra (δ ppm) of **9** were characterised by the presence of two doublets (J = 4Hz) near 4.7 and 4.3 assignable to H-5 and H-7 respectively, in addition to two doublets at 3.5 corresponding to H-6. On the basis of the value of the coupling constant the cycloadducts, **9a-c** were assigned the indicated trans-configura-tion.[4]

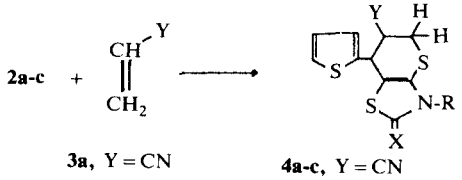
Results of antimicrobial tests are shown in Table I. It reveals that **2a** and **5a** have significant activity against *B. cereus, Mycobacterium* sp. and *Actinomyces* sp.



1
a, R = H; X = S
b, R = H; X = O
c, R = C_6H_5; X = O

2a-c

Scheme 1



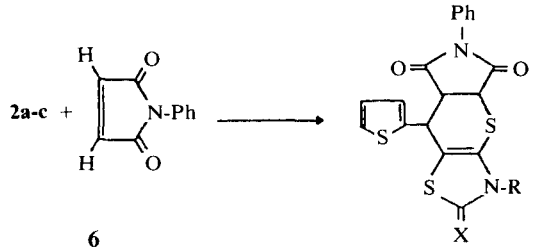
2a-c

3a, Y = CN
b, Y = COOEt

4a-c, Y = CN
5a-c, Y = COOEt

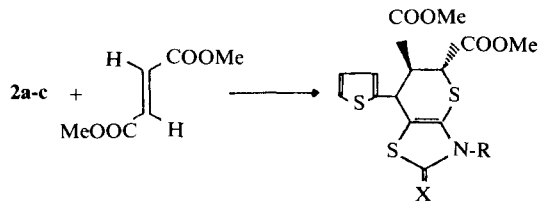
Scheme 2

§To whom all correspondence should be addressed.



6 7a-c

Scheme 3



8 9a-c

Scheme 4

Table I. Antimicrobial activities *in vitro*

Organism	2a	2b	2c	4b	4c	5a	5b	5c	7a	7c
E. coli	–	–	–	–	–	–	–	–	–	–
B. cereus	+ + +	–	–	–	–	–	–	–	–	–
B. subtilis	+	–	–	–	–	+ + +	–	–	–	–
Sarcina sp.	–	–	–	–	–	–	–	+ +	–	–
Mycobacterium sp.	+ + +	+ + + +	+ + +	–	–	+ + + +	–	–	–	–
Saccharomyces sp.	–	–	–	–	–	–	–	–	–	–
Actinomyces sp.	+ + + +	–	–	–	–	+ + + + +	–	–	–	–
Micrococcus sp.	–	–	–	–	–	–	–	–	–	–

Inhibition zone around the disc (each disc contains 100 μg): + = 3 mm, + + = 5 mm, + + + = 8 mm, + + + + = 13 mm, + + + + + + = 21 mm.

Table II. Compounds 2 and cycloadducts 4, 5, 7 and 9

Compound*	M.P. (°C)	Yield (%)	Formula	Elemental analysis (%)					
				Calc.			Found		
				C	H	S	C	H	S
2a	240	85	$C_8H_5NS_4$	39.5	2.07	52.6	39.2	2.00	52.2
2b	227	80	$C_8H_5NOS_3$	42.3	2.22	42.2	42.0	2.10	42.0
2c	200	85	$C_{14}H_9NOS_3$	55.5	2.99	31.6	55.2	2.81	31.3
4a	210	65	$C_{11}H_8N_2S_4$	44.6	2.72	43.2	44.2	2.70	43.1
4b	202	70	$C_{11}H_8N_2OS_3$	47.2	2.88	34.3	47.0	2.80	34.1
4c	180	65	$C_{17}H_{12}N_2OS_3$	57.3	3.40	26.9	57.1	3.32	26.5
5a	194	65	$C_{13}H_{13}NO_2S_4$	45.5	3.82	37.4	45.4	3.80	37.2
5b	204	60	$C_{13}H_{13}NO_3S_3$	47.7	4.00	29.4	47.5	3.84	29.2
5c	139	70	$C_{19}H_{17}NO_3S_3$	56.5	4.25	23.8	56.2	4.11	23.6
7a	217	75	$C_{18}H_{12}N_2O_2S_4$	51.9	2.91	30.8	51.7	2.79	30.6
7b	182	70	$C_{18}H_{12}N_2O_3S_3$	54.0	3.02	24.0	54.0	2.92	23.8
7c	194	65	$C_{24}H_{16}N_2O_3S_3$	60.5	3.39	20.2	60.2	3.38	20.0
9a	203	70	$C_{14}H_{13}NO_4S_4$	43.4	3.35	33.1	43.2	3.25	32.8
9b	186	70	$C_{14}H_{13}NO_5S_3$	45.3	3.50	25.9	45.1	3.42	25.7
9c	134	65	$C_{20}H_{17}NO_5S_3$	53.7	3.83	25.8	53.8	3.71	25.6

*All compounds were crystallised from ethanol except **2a-c**, **9a** and **5c** from glacial acetic acid.

EXPERIMENTAL

The melting points are uncorrected. The IR spectra were recorded on Pye Unicam SP-1100 spectrophotometer using KBr disc. ^{1}H-NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. The microanalyses were performed by the microanalytical center at Cairo University.

Preparation of 5-(2-thienyl)methylene-2-thiazolidinone-4-thiones (2a-c)

Equimolar amounts (0.01 mole) of **1a-c** and thiophene-2-carboxaldehyde in glacial acetic acid and in presence of anhydrous sodium acetate (0.01 mole) were stirred on a water bath for 1 hr and left to cool, to afford the coloured products, **2a-c**. The crude products were crystallised from glacial acetic acid. The physical and spectral data of the products are listed in Tables II and III, respectively.

General procedure for the reaction of 2a-c with acrylonitrile, ethyl acrylate, N-phenylmaleimide and dimethyl fumarate

A solution of equimolar amounts (0.01 mole) of each of **2a-c** and the appropriate dienophile in glacial acetic acid (30 m*l*) was refluxed for 1 hr and then left overnight. The white solid so formed was filtered off and crystallised from ethanol or glacial actic acid. The physical constants and spectral data of the cycloadducts **4, 5, 7** and **9** are listed in Tables II and III.

Methods used in biological tests

Different strains of bacteria, actinomycets and fungi were used as test organisms. A solid nutrient medium was used for bacteria and for yeast. The

Table III. Spectral data of compounds 2, 4, 5, 7 and 9

Compound	IR (cm^{-1})	^{1}H-NMR (δ ppm)
2a	3225 (NH), 3050 (−HC=CH) and 1175 (C=S)	—
2b	3200 (NH) and 1680 (C=O)	10.9 (s, 1H, NH), 7.2-6.8 (m, 3H) and 7.65 (s, 1H, −CH=).
2c	1680 (ring C=O).	—
4a	3200 (NH) and 2220 (C≡N)	11.1 (s, 1H, NH), 7.1-6.8 (m, 3H) 4.75 (d, 1H, H-7), 2.7 (d, 1H, H-5) 3.53 (d, 1H, H-5) and 4.0-3.6 (m, 1H, H-6).
4b	3220 (NH), 2220 (C≡N) and 1680 (ring C=O).	—
4c	2220 (C≡N) and 1680 (C=O)	7.3-6.8 (m, 8H), 4.75 (d, 1H, H-7) 2.7 (d, 1H, H-5), 3.5 (d, 1H, H-5) and 4.0-3.62 (m, 1H, H-6).
5a	3200 (NH) and 1720 (ester C=O).	11.2 (s, 1H, NH), 7.1-6.8 (m, 3H) 2.8 (d, 1H, H-5), 3.55 (d, 1H, H-5) 3.9-3.6 (m, 1H, H-6), 4.7 (d, 1H, H-7), 4.4 (q, 2H, $\underline{CH_2}CH_3$) and 1.4 (t, 3H, $CH_2\underline{CH_3}$).
5b	3200 (NH), 1710, 1680 (ester and ring C=O).	—
5c	1710 and 1680 (ester and ring C=O).	7.3-6.9 (m, 8H), 4.70 (1H, H-7), 2.7 (d, 1H-H5), 3.5 (d, 1H, H-5) 4.1-3.61 (m, 1H, H-6), 4.3 (q, 2H $\underline{CH_2}CH_3$) and 1.4 (t, 3H, $CH_2\underline{CH_3}$).
7a	3200 (NH) and 1740 (amide C=O).	—
7b	3200 (NH) and 1740, 1680 (amide and ring C=O).	11.1 (s, 1H, NH), 7.4-6.8 (m, 8H), 5.35 (d, 1H, H-7), 5.15 (d, 1H, H-5), and 4.0 (dd, 1H, H-6).
7c	1740 and 1680 (amide and ring C=O).	7.3-6.8 (m, 13H), 5.3 (d, 1H, H-7) 5.1 (d, 1H, H-5) and 4.1 (dd, 1H, H-6).
9a	3200 (NH) and 1770 (ester C=O).	11.3 (s, 1H, NH), 7.1-6.8 (m, 3H) 4.3 (d, 1H, H-7), 4.7 (d, 1H, H-5) 3.55 (dd, 1H, H-6) and 3.8 (s, 6H, 2 CH_3).
9b	3180 (NH) and 1780, 1690 (ester and ring C=O).	—
9c	1780 and 1680 (ester and ring C=O).	—

media described by Wickerham.[5] The method used for detection of the antimicrobial activity of the test compound was the diffusion plate method described by Greenwood,[6] and Peach and Tracey.[7] Each pore received about 0.1 m/ equivalent to 100 μg of the test compound.

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