Nucleophilic substitution of N-(p-substituted phenyl)-3-bromomethyl-5-methyl-4,6-dihalo-1,1-dioxo-1,2-thiazines with sodium sulfide

Mohamad.H.A. and Burhan A. Saleh

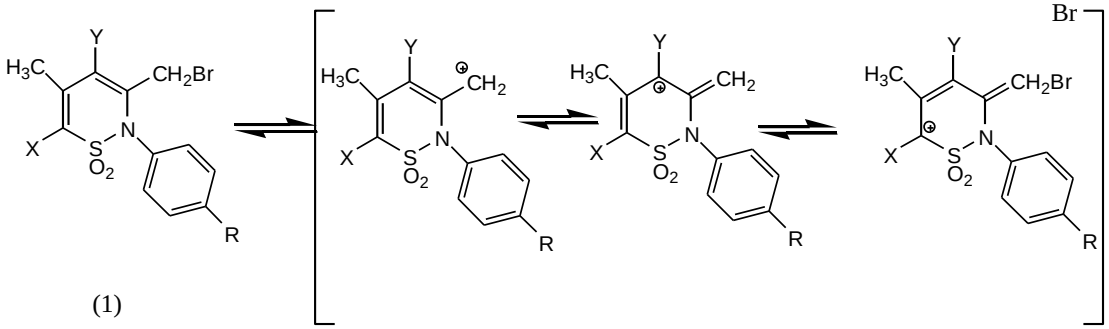
Department of Chemistry, College of Science, University of Salahdden, Erbil, Iraq

Abstract:

Mono-and dihalide derivatives of N-(-p-substituted phenyl)-3-bromomethyl-5-methyl-4,6-dihalo-1,1-dioxo-1,2-thiazines (1) were refluxed with sulfide anion solution in aceton, a series of new fused hetrocyclic compounds were obtained, which are biologically active. The structures of the new compounds were studied by elemental analysis, UV, Vis, IR and ^{1}H-NMR spectroscopy.

Introduction:

Thiazines of the type (1) that contains 3-bromomethyl group are very reactive toward nucleophilic substitution reaction [1]. In their reactivities behaves analoge to benzyl halides especially in the accommodation of the positive charge that generated during the reaction by thiazinyl system (benzyl system) through many positions of the thiazine ring [1].



(1)

X= H, Br, Br, Cl, Cl
Y= H, H, Br, H, Cl
R= H, CH3, OCH3, Br

The aim of this work is to synthesize new thioethers according to the common equation:

$$2\ R\text{-}CH_2Br + Na_2S \longrightarrow RCH_2\text{-}S\text{-}CH_2R + RCH_2\text{-}S\text{-}S\text{-}CH_2R \quad (2)$$

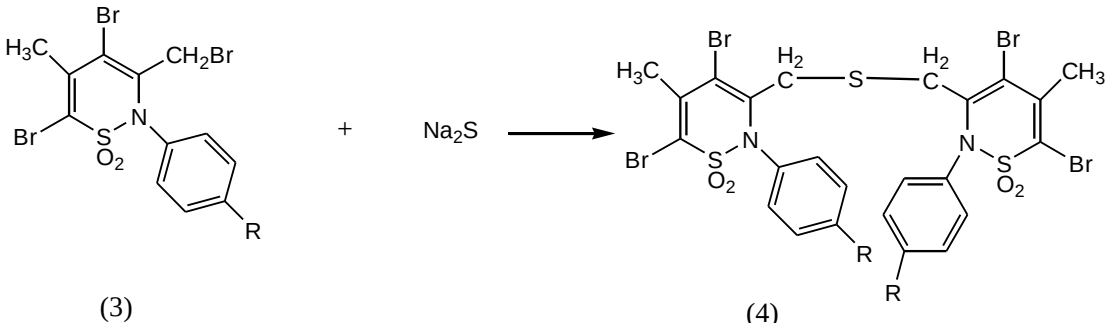
But the result of the reaction showed other products rather than that expected thioether (see later).

Result and discussion:

Symmetrical sulfides are commonly synthesized by treatment of two moles of the appropriate alkylhalide with sodium sulfide under various reaction conditions [2].

The reaction may be carried out intermolecular by addition of sulfide ion to1,3-; 1,4-or 1,5- dihalide to give four, five or six membered by sulfur containing hetrocyclic rings [3, 4].

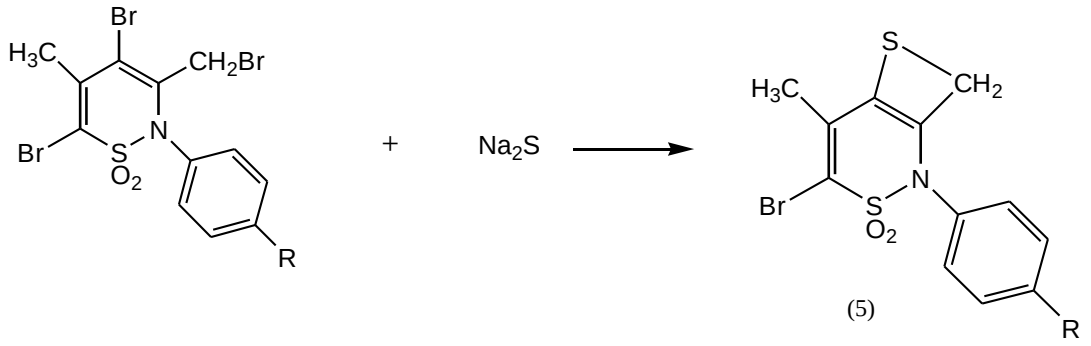
In the present work different N-(p-substituted phenyl)-3-bromomethyl-5-methyl-4,6-dibromo-1,1-dioxo-1,2-thiazines were treated with sodium sulfide in aceton as reaction medium to obtain the corresponding thioethers according to the following common equation:



(3) (4)

R= H, CH_3, OCH_3, Br, Cl

The element analyses of the obtaind products didn't agree with those theoretically calculated value for compounds (4) (Table1). It was found that the element analysis shows the absence of two bromine atoms rather than one from the product molecule (Table1). This fact let us to suggest for the structure of the obtained compounds the assumption that an intramolecular cyclazation had taken place via an initial formation of the sulfide anion.



(5)

Table 1: Elemental analysis of the prepared compounds 5, 5a,b,c,d and 6, 6a,b,c

Comp. no.	Formula	C%		H%		N%	
		Found	Calcu.	Found	Calcu.	Found	Calcu.
5	$C_{12}H_{10}NO_2S_2Br$	42.08	41.86	2.78	2.92	3.96	4.00
5a	$C_{13}H_{12}NO_2S_2Br$	44.20	43.58	3.72	3.37	4.22	3.90
5b	$C_{13}H_{12}NO_3S_2Br$	42.66	41.71	3.83	3.23	3.69	3.74
5c	$C_{12}H_9NO_2S_2ClBr$	38.03	37.95	2.70	2.38	3.82	3.68
5d	$C_{12}H_9NO_2S_2Br_2$	34.89	33.98	2.66	2.13	3.53	3.30
6	$C_{12}H_{10}NO_2S_2Cl$	48.13	48.07	3.29	3.36	4.53	4.67
6a	$C_{13}H_{12}NO_2S_2Cl$	49.71	49.89	3.09	3.83	4.44	4.47
6b	$C_{13}H_{12}NO_3S_2Cl$	48.36	49.75	3.15	3.85	4.32	4.46
6c	$C_{12}H_9NO_2S_2Cl_2$	45.09	45.01	2.77	2.84	4.22	4.38

Compounds of type2 are considered to belong to fused ring system between theit and thiazinering. The information's obtained from ^{1}H-NMR and IR-spectroscopy and elemental analysis are in good agreement with the suggested structures. ^{1}H-NMR spectrum (Table2) shows absorption signal at δ2.5 ppm attributed for C5-CH_3; at δ 2.95 ppm (s) for C3-CH_2-S and multipete at δ 7-7.5 ppm for the aromatic protons. The IR-spectrum (Table3) showed two strong bands at 1135, 1340 cm^{-1} corresponding to symmetrical and asymmetrical SO_2- group stretching and weak bands at 630-705 cm^{-1} corresponding to stretching C-S bond. For the formation of such fused system the following mechanism might be suggested however more studies are still necessary to confirm the actual structures of the products especially by ^{13}C-NMR spectroscopy and single crystal X-ray diffraction studies:

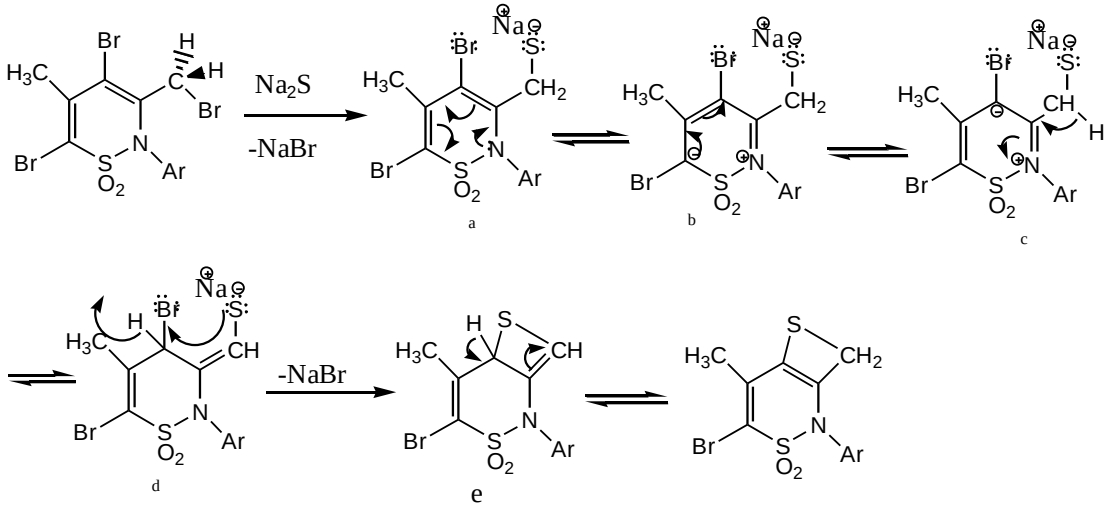


Table 2: 1H-NMR Data of the synthesized compounds in ppm*

Comp. no.	δ	Intensity	Multiplicity	Assignments
5	2.0	3	S	For CH_3- group attached to C_5
	2.95	2	S	For CH_2-S protons attached to C_3
	7-7.5	5	M	Five aromatic protons of phenyl group
5a	1.95	3	S	For CH_3- group attached to C_5
	3.35	3	S	p-CH_3 protons on the phenyl ring
	3.8	2	S	For CH_2-S protons attached to C_3
	6.75-7.3	2:2	d,d	Four aromatic protons of phenyl group
5b	2	3	S	For CH_3- group attached to C_5
	3.35	2	S	For CH_2-S protons attached to C_3
	3.8	3	S	O-CH3 protons at p-position of the phenyl ring
	6.75-7.3	2:2	d, d	Four aromatic protons of phenyl group
5c	1.9	3	S	For CH_3- group attached to C_5
	2.95	2	S	For CH_2-S protons attached to C_3
	6.8-7.2	2:2	d,d	Four aromatic protons of phenyl group
5d	2	3	S	For CH_3- group attached to C_5
	3.05	2	S	For CH_2-S protons attached to C_3
	6.5-7	2:2	D,d	Four aromatic protons of phenyl group
6	1.9	3	S	For CH_3- group attached to C_5
	3.2	2	S	For CH_2-S protons attached to C_3
	6.8-7.12	5	M	Five aromatic protons of phenyl group
6a	1.95	3	S	For CH_3- group attached to C_5
	2	2	S	For CH_2-S protons attached to C_3
	3.15	3	S	p-CH_3 protons on the phenyl ring
	6.07-7.0	2:2	D,d	Four aromatic protons of phenyl group
6b	2.05	3	S	For CH_3- group attached to C_5
	3.6	2	S	For CH_2-S protons attached to C_3
	4.0	3	S	p-CH_3 protons on the phenyl ring
	6.8-7.7	2:2	D,d	Four aromatic protons of phenyl group
6c	2	3	S	For CH_3- group attached to C_5
	3.4	2	S	For CH_2-S protons attached to C_3
	7.0-7.07	2:2	d,d	Four aromatic protons of phenyl group

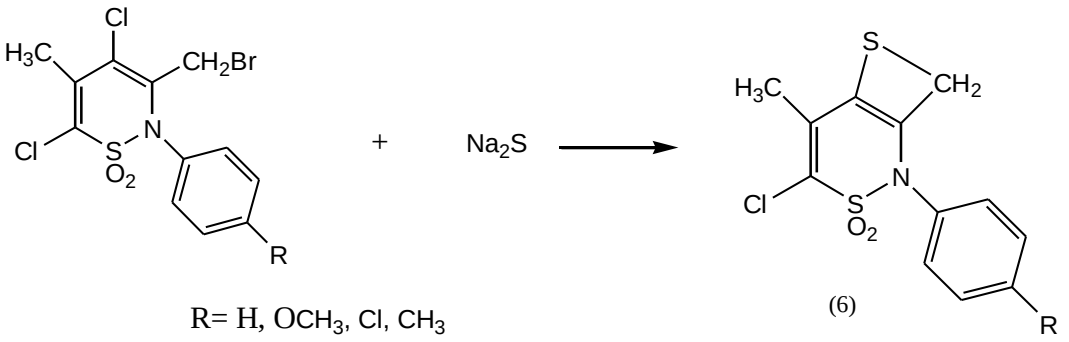
*Solvent used DMSO-d^6

Table 3: IR Data of the prepared compounds in cm^{-1}:

Comp. no.	SO_2	C=C	S-C	C-O
5	1130, 1338	1590	675-695(w)	
5a	1135, 1340	1600	630-690(m)	
5b	1140, 1345	1600	660-700(w)	1010, 1240(s)
5c	1145, 1340	1605	645(m)-690(w)	
6	1135, 1340	1555	630(m)-705(w)	
6a	1160, 1335	1585	680-700(m)	
6b	1135, 1340	1605	635-675(m)	980-1230
6c	1140, 1345	1600	630-700(m)	
6d	1130, 1340	1600	640-690	

Sodium sulfide, as ion pair, tends to attack as nucleophil on theCH_2-Br group bonded to C-3 of the ring to form an intermediate compound (a) after elimination of NaBr molecule, which due to geometrical requirement could rearrange to the tautomeric from (e). Of course the counter Na^+-ion plays a great role in addition to the unshared pair of electrons on the adjacent nitrogen to facilate the tautomerization process. By this way the rehybridization of C-4 atom, which hold the second bromine atom, from sp^2 to sp^3 could be possible as illustrated from the canonical structure(a-e). Now the mercaptide anion in (c) or (d) is in the proper position to attack C4-Br, displacing the bromide ion and finally to give compound (5). In addition the thin layer chromatography of the recrystallized product shows only one spot indicating the formation of only one product.

Using the same way a wide range of N-(P-substituted aryl)-5-methyl-6-bromo-[3,4.e]-thiete-1,1-dioxo-1,2-thiazines could be obtained (see table 4 and 5). Not only the bromine atom at C-4 could displaced by the mercapto anion to form fused thiete-thiazine system, but chlorine atom, also, could be displaced by the same way however chlorine is relatively less displaceable, as leaving group, than bromine. So two types of mixed halogenated thiazines were prepared [5] and both types were treated, by the same way, with sodium sulfide to obtain the corresponding thiete-thiazine system that contain in a chlorine atom at position 6 of the thiazin ring as it is shown from the following equation:



R= H, OCH_3, Cl, CH_3

(6)

Table (4): Percentage yield and and physical properties of the prepared thiets (5a-5d):

Comp. no.	R	M.P.˚C	Yield %	Rf. (1But:3MeOH)	Color	λ max (nm)
5	H	135-137	25	0.75	Dark brown	327-270
5a	CH3	150-152	30	0.67	Dark brown	320-268
5b	OCH3	138-140	46.5	0.50	Brown	322-274
5c	Cl	161-163	54.4	0.36	Brown	318-268
5d	Br	170-173	49.6	0.68	Brown	318-271

Table (5): Percentage yield and physical properties of the prepared thiets (6a-c):

Comp. no.	X	M.P.˚C	Yield %	Rf. (1But:3MeOH)	Color	λ max (nm)
6	H	132-134	60.8	0.126	Dark brown	309-254
6a	CH3	142-144	46.8	0.291	Brake	349-273
6b	OCH3	145-148	40.5	0.428	Brown	332-274
6c	Cl	175-177	80.0	0.324	Brown	340-274

A suggested sterical structure for compound 5 was drawn by CS Chem draw ultar program based on the single crystal X-ray developed structure of N-aryl-3,5-dimethyl-1,1-dioxo-1,2-thiazine [6] are shown in (Fig 1).
The Antibacterial activities of some of the prepared compounds are shown in table(6).

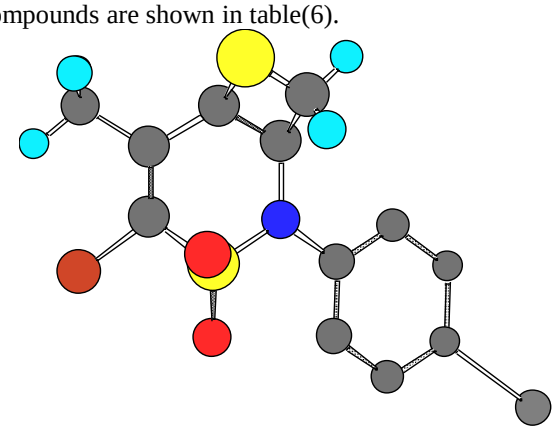


Figure (1): Suggested sterical molecular structure of compound (5) drawn by CS-Chem Drraw Ultra program based on the single crystal X-ray results for structure of N-aryl-3,5-dimethyl-1,1-dimethyl-1,1-dioxo-1,2-thiazine[5].

Experimental section:

The IR spectra were recorded as KBr-discs using a Pye-Unicom SP-300S infrared spectrophotometer; UV-spectra of the compounds were measured in DMSO using PU 8800 UV/VIS spectrophotometer; 1H-NMR spectra were recorded using Varrian A-60 MHz instrument TMS as internal standard (at Mousl University-Iraq). The melting points were measured on a Gallenkamp melting point apparatus and are not corrected. Elemental analysis of the synthesized compounds were obtained on Karlo Erba Type 1106.

Preparation of the starting materials:

The necessary N-(-p-substituted phyenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazines were prepared according to procedures placed by Helferich and Coworkers [7]. With modification done by Brahim[8].
The prepared thiazines were halogenated with NBS or SO2CL2 for purposes of this work [5,9,11,12] as it is illustrated in the following scheme.

Synthesis of N-(-p-substituted aryl)- 5-methyl-6-bromo-[3,4,e]-thiete-1,1-dioxo-1,2-thiazines:

To a solution of N-(-p-substituted aryl)-3-bromomethyl-5-methyl-4,6-dibromo-1,1-dioxo-1,2-thiazines (0.001Mole) in acetone, 0.078g (0.001 Mole) sodium sulfide was added. The mixture was refluxed on a water bath for one hour to give a colored solution. The mixture was filtered before cooling to room temperature; methanol was added and colored precipitate was obtained, which then recrystallized from methanol.

Synthesis of N-(-p-substituted aryl)- 5-methyl-6-chloro-[3,4,e]-thiete-1,1-dioxo-1,2-thiazines:

A mole ratio (1:1) of N-(-p-substituted aryl)-3-bromomethyl-5-methyl-4,6-dichloro-1,1-dioxo-1,2-thiazines and sodium sulfide in (25ml) acetone was refluxed on a water bath for (1.5)hour to give a colored solution. The mixture was filtered off and the solvent was let to evaporate at room temperature and the residue was recrystallized from methanol.

Table 6: Antibacterial activities of some prepared compounds

Comp. no.	Activity against *Klebseela*	Activity against *Staphylococcus*
5b	+	+
6a	+	+
6b	+	+

References:

1-E. Fanghanei, H. Mohammed and Y. Keita. J. Prakt. Chem., 324(3) 353(1982), C. A. 83, 7589C, 1960.
2-A. Johan, H. Iabuschange, I. S. Malherbo and C. J. Merer. Tetrahedron latters, 93, 3571, (1976).
3-E. N. Karaulova. Russian Chemical Reviews, 56(6), 546, (1987).
4-F. Hisashi. Hetrocycles, 16(10), 170, (1981); CF. Chem. Abstr. 76, 99497w, (1972). H. I. Furukawa, Chem. Abst. 96, 6702j, (1982).
5-E. Fanghanel, R. Radeglia, H. Mohammed. J. Prakt. Chem. 326(4), 545, (1984)
6-N. B. Buttrus, H. A. Mohammed. Iraq. J. of Chem. 5(3), 256, (1990).
7-B. Heferich, R. Dehein, K. Geist, H. Junger and D. Wiele. Liebigs. Ann. Chem. 32, 646, (1961).
8-R. R. Brahim. M. Sc.thesis, Salahaddin University, Erbil-Iraq (1997).
9-N. M. Younis. M. Sc.thesis, Salahaddin University, Erbil-Iraq (1995).
10- E. Fanghanel, H. Muhummed, Richter andreas. East german patent 205-900 (C07D279/02).
11- A. Mohammed and N. M. Yonis. Zanco, Special issue (1), 254, (1997).
12- A. Mohammed and N. M. Yonis. Zanco, Special issue (2), 353, (1997).

تفاعلات الاستبدال النيوكلوفيلي لمركبات N-(P-substituted phenyl)-3-bromomethyl-1-5 methyl1-4,6-dihalo-1,1-dioxo-1,2-thiazines مع كبريتيد الصوديوم

حسن احمد محمد و برهان احمد صالح

قسم كيمياء، كلية العلوم، جامعة صلاح الدين، اربيل، جمهورية العراق

الملخص:

تم تصعيد المشتقات الاحادية والثنائية الهالوجين لمركبات N-(P-substituted phenyl)-3-bromomethyl-1-5 methyl1-4,6-dihalo-1,1-dioxo-1,2-thiazines مع محلول لايون السلفايد في الاسيتون وتم الحصول على سلسلة من المركبات الجديدة ذوات الحلقات الملتحمة و جميعها فعالة بايولوجيا. تمت دراسة تراكيب المركبات الجديدة بالاستعانة بتحاليل العناصر، اطياف الاشعة فوق البنفسجية، اشعة تحت الحمراء و طيف الرنين النووي المغناطيسي 1H-NMR.