Synthesis of New Schiff Bases and 2,3-Disubstituted - 1,3-Thiazolidin-4-one Derivatives Containing Benzothiazole Moiety

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Abstract

Two series of Schiff Bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives were synthesized . Reaction of 2-mercaptobenzothiazole with α-chloro acetic acid gave compound[I]. Esterification of carboxylic moity of compound [I] , using absolute methanol in the presence of conc . H_2SO_4 yielded acorresebonding ester [II] , wich was condensation with hydrazine hydrate to give acid hydrazide [III] . The new Schiff bases $[V]_n$ were synthesized by reaction of acid hydrizide with dialdehyde $[IV]_n$ in the presence of glacial acetic acid . The thiazolidinone derivatives $[VI]_n$ have been obtained from the azomethines through the addition of thioglycolic acid . Their chemical structures have been confirmed by melting points , FTIR and ^{1}HNMR (of some of them) .

Benzothiazole , thiazolidinone.

Introduction

Thiazolidin-4-one derivatives have attracted a great deal of interest due to their antibacterial [1-3] , anti-infammatory [4] , fungicidal activity [5], Antifeedant activity, Acaricidal activity, Contact toxicity, and Stomach toxicity [6]. Over views of their synthesis , properties reactions and applications have been published [7,8] .

Benzothiazole derivatives have been reported to have broad range of biological activities [9-11] .

These findings focused particular interest on incorporating thiazolidinone and 2-mercaptobenzothiazole in one framework , which could be useful for biological and pharmacological screening.

Experimental

Materials : Most of chemicals used were supplied from Fluka , Merck and BDH Chemicals Co. and used as received .

Techniques: Uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus. FTIR spectra in the range 500-4000cm^{-1} were obtained by using potassium bromide discs on FTIR instrument Model 8000 Shimadzu Spectrophotometer, Japan . ^{1}HNMR spectra were taken on company : Bruker , model: ultra shield 300 MHz Spectrophotometer using DMSO as a solvent with TMS as an internal standard and elemental analysis (C.H.N) were carried out by EA-017.

Synthesis of compounds

The reaction sequence leading to the formation of new compounds $[V]_n$ and $[VI]_n$ are outlined in Scheme 1.

2-Mercapto acetic acid benzothiazole [I]

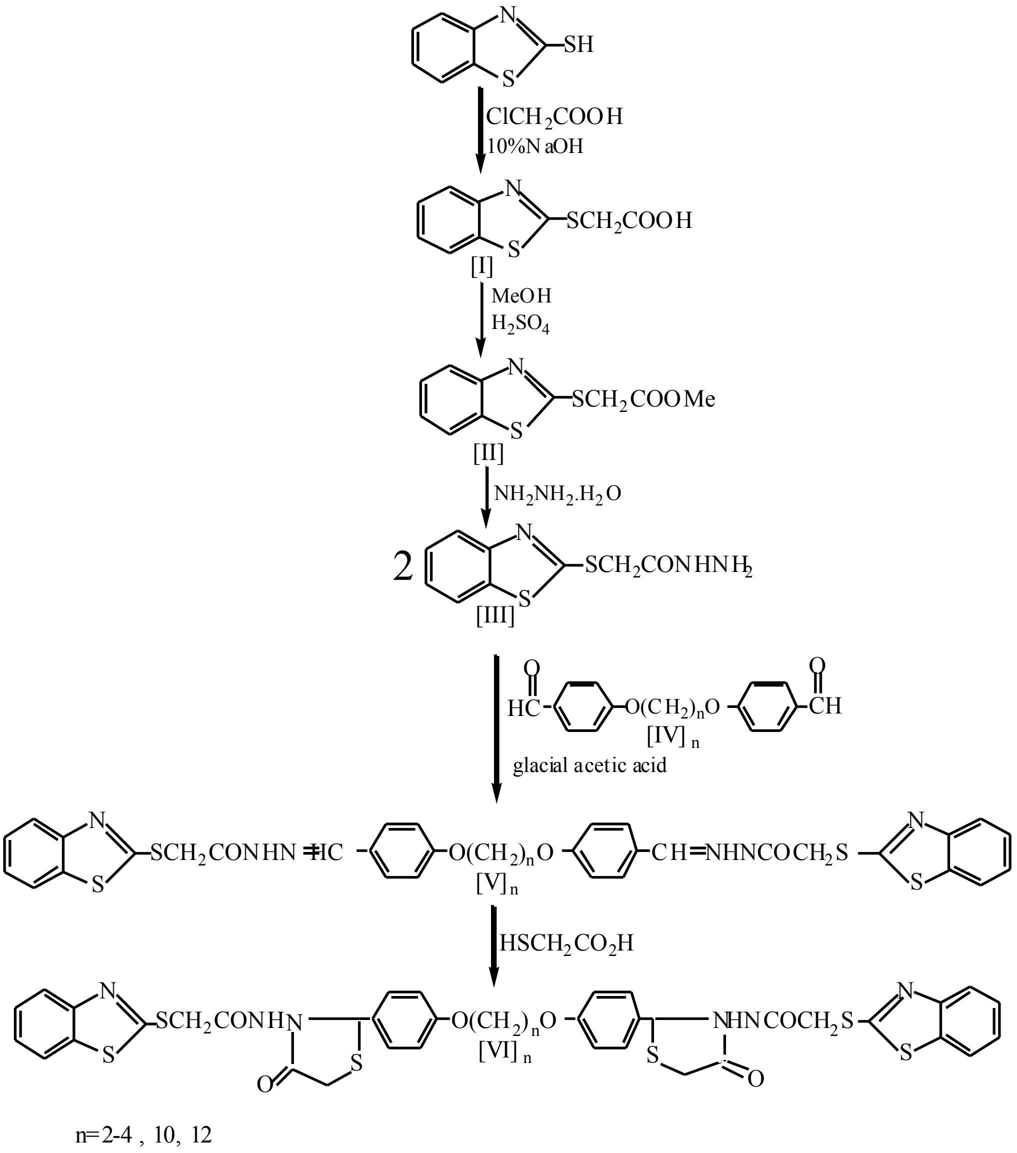
To a stirred mixture of α-chloro acetic acid (0.01mol) and 10% aqueous sodium hydroxide (10 mL), a solution of 2-mercaptobenzothiazole (0.01mol) in 10% aqueous solution of sodium hydroxide(10 mL) was added . The mixture was refluxed for three hours. After cooling, the solution was acidified with concentrated hydrochloric acid. The precipitate was filtered and recrystallized from ethanol [12] to yield 90%, m.p=155°C.

2-(methylthioacetate) benzothiazole ester[II] : was prepared following the procedure described by A. Vogel [13].

2-(thioacetyl hydrazide) benzothiazole [III] This compound was prepared according to references [14] .

Polymethylene-α,ω-bis-4-oxybenzaldehyde $[IV]_n$

In a 100 mL flask ,4-Hydroxybenzaldehyde (2.44gm , 0.02 mol) was dissolved in 15mL of DMF. Anhydrous sodium carbonate (0.025mol) and (0.01mol) of the appropriate α,ω –dibromo or dichloro alkane were added to the reaction flask . The stirred mixture was refluxed for 4hrs , allowed to cool , and then poured into 400 mL of cold water , cooled at 5°C overnight , and then filtered , washed well with water , dried in air , recrystalized from ethanol(15), yield 88-98% .



Scheme 1

α,ω-bis-[(2-thioacetylhydrazidebenzothiazole-2-yl)benzylidene-4-oxy]alkane $[V]_n$

A mixture of compound[III] (0.02mmol) , dialdehyde $[VI]_{n=2}$ (0.01mmol) , three drops of glacial acetic acid and absolute ethanol (10mL) was refluxed for 4 hours. The reaction mixture was concentrated , cooled and the formed precipitate was filtered off, dried and then recrystallized using chloroform to give pale yellow [16], Yield (80%) , m.p=210 °C.

Likewise other compounds [V] with n=3,4,10,12 (were prepared in a same way using dialdehyde $[IV]_n$ with different n=3,4,10,12) .Characterization data are presented in table 1.

Polymethylene-α,ω-bis-[N-(2-thioacetylhydrazinebenzothiazole) -4-oxo-1,3-thiazolidin-2-(p-oxybenzene)] $[VI]_n$

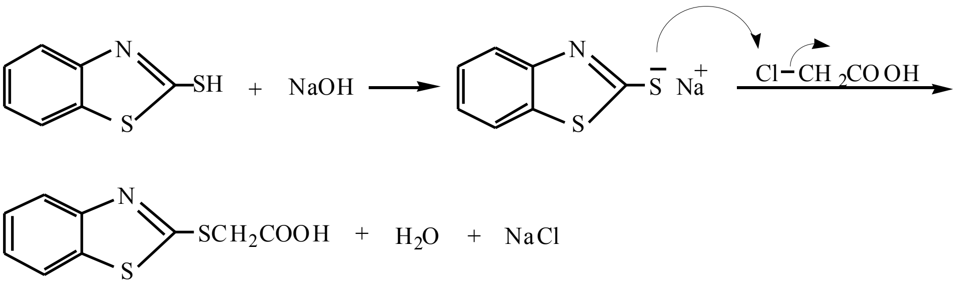
A mixture of Schiff base $[v]_n$(0.01mmol), thioglycolic acid (0.022mmol) was refluxed in dry benzene 6mL for 6 hours . The solvent was evaporated and the reaction mixture was neutralized with cold dilute sodium bicarbonate solution , the formed product was filtered off and recrystallized from acetone to yield 70% , m.p=188-190 °C.

Likewise other compounds [VI] with n=3,4,10,12 (were prepared in a same way using Schiff bases $[V]_n$ with different n=3,4,10,12) .Characterization data are presented in table 3.

Results and Discussion

The reaction between 2-mercaptobenzothiazole and α-chloroacetic acid in alkali media was used to prepare the compound [I]. The α-halogroup in α-chloroacetic acid is good leaving group and sulfur compounds are a good nucleophile. Thus, the reaction is a typical of the nucleophilic substitution reaction of the thiol group , where the α-halo group could be replaced easily in this reaction to get good yield[17].

The mechanism of this reaction may be outlined as follows, Scheme (2).



Schem 2

The structure of this compound [I] was studied by its melting point 155 °C and FTIR spectrum , which showed broad band at 2750-3390cm^{-1} due to νO-H group , sharp peak at 1690 cm^{-1} assigned to carbonyl group of carboxylic moity and the aliphatic C-H stretching at 2950 cm^{-1} . also showed significant bands in the region (3060 , 1575 , 1454 and 750) cm^{-1} that indicated the presence of benzothiazole moiety. 2-(Methylthioacetate) benzothiazole[II] was obtained by esterification of the carboxylic acid moity of compound [I] using absolute methanol with conc. H_2SO_4 was identified by FTIR spectrum . FTIR spectrum showed disappearance of two peaks of νOH and νC=O of carboxylic moiety of compound [I] together with the appearance of good peak at 1705 cm^{-1} which could be attributed to νC=O of ester group.

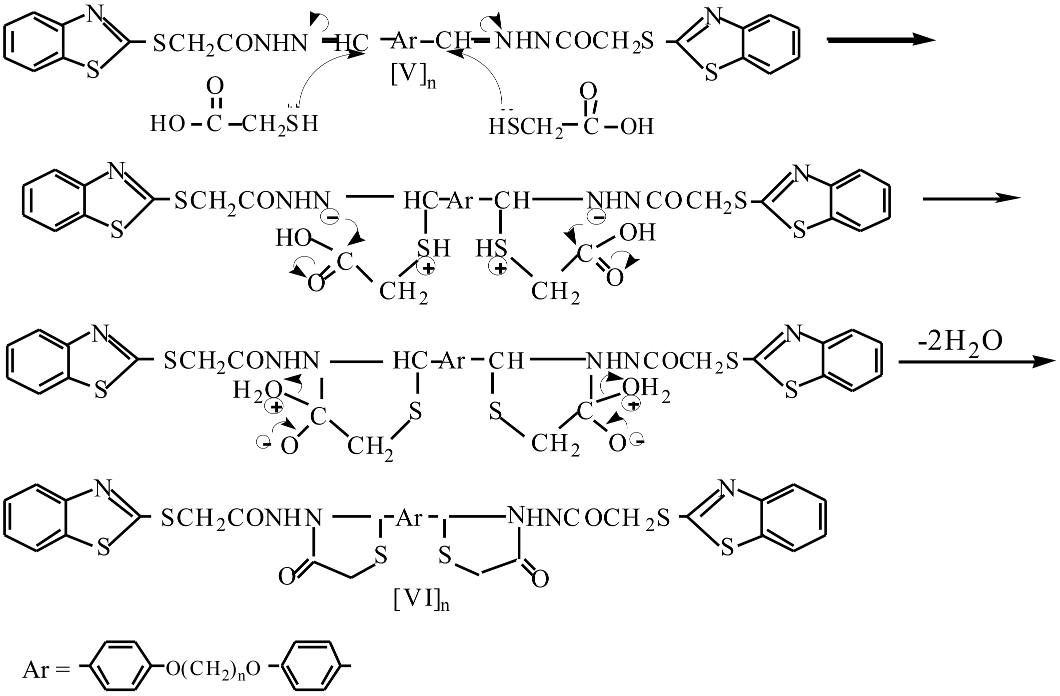
Condensation of ester [II] with hydrazine hydrate yielded the 2-(thioacetyl hydrazide)benzothiazole [III] which is characterized by its melting points 120°C . FTIR spectra , showed the following absorption bands: νC=O of amide group at 1645 cm^{-1}, bands in the regions (3460, 3282, 3197) cm^{-1} due to asymmetric and symmetric stretching vibration of NH , NH_2 groups , respectively. The spectra showed band at 2928 cm^{-1} assignable to the stretching of aliphatic (C-H).

The Schiff bases of series $[V]_n$ were prepared by refluxing of compound $[III]_n$ with dialdehyde $[IV]_n$ (which are obtained from the reaction of 4-hydroxybenzaldehyde with α,ω-dibromo or dichloro alkane using DMF as the solvent in Na_2CO_3 medium) in glacial acetic acid as a catalyst.

These compounds series $[V]_n$ are characterized by FTIR and ^{1}HNMR spectroscopy . FTIR spectra showed the disappearance of two absorption bands due to NH_2 stretching of compound [III] together with the appearance of a band at (1614-1616) cm^{-1} assignable to imine group (CH=N) . The spectra also shows the bands at (2840-2954) cm^{-1} is due to aliphatic C-H stretching. Table 2 exhibited the characteristic FTIR absorption bands of these compounds

^{1}HNMR spectrum of compound $[V]_{n=2}$ (DMSO as a solvent) showed single broad peak at δ 9.15 ppm that could be attributed to the two protons of NH , a multiplet signal at δ 7.0-7.55 ppm for eight aromatic protons of the phenyl rings of benzothiazole moiety and a doublet of doublets at δ 7.8-8.25 ppm for eight aromatic protons of two benzene rings . The imine protons appeared at δ 4.92 ppm . The ^{1}HNMR spectrum also showed the a singlet at δ 4.65 ppm assigned for four protons of the mercapto methylene groups to (SCH_2) and triplet signal between δ 3.80-3.92 ppm that could be assigned to the four protons of methylene group ($O-CH_2$)

2,3-Disubstituted-1,3-thiazolidin-4-ones$[VI]_n$ were obtained by reacting the Schiff bases $[V]_n$ with thioglycolic acid acid in dry benzene and reflux for 6hrs. The mechanism of this reaction may be outlined as follows, Schem (3).



Scheme 3

The structural assignments of these compounds $[VI]_n$ was based on spectral data FTIR and ^{1}HNMR spectroscopy . The FTIR exhibited significant bands at 3210 cm^{-1} and 1730 cm^{-1} which could be attributed to NH stretching and C=O stretching of thiazolidinone ring , respectively . Besides this , a band about 1660 cm^{-1} is due to C=O (amide) stretching and disappearance of absorption stretching band due to imine group . Table 4 exhibited the characteristic FTIR absorption bands of these compounds.

^{1}HNMR spectrum of compound $[VI]_{n=2}$, figure (1) showed the following characteristics chemical shifts (DMSO as a solvent) singlet at δ 11.5 ppm could be attributed to the two protons of NH groups , a multiplet signal at δ 7.05-7.5 ppm for eight aromatic protons of the phenyl rings of benzothiazole moiety and a doublet of doublets at δ 7.65-8.2 ppm for eight aromatic protons of two benzene rings . A sharp singlet was abserved at δ 4.80 ppm that could be assingned to the four protons of the mercapto methylene groups (SCH_2) . A singlet signal appeared at δ 4.65 ppm for four protons of H-5 thiazolidinone . The triplet signal observed between δ 4.2-4.49 ppm was assinged to four protons of methylene group ($O-CH_2$) showed singlet signal at δ 6.66 ppm that could be attributed to the two protons of H-2 thiazolidinone (2).

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Table (1): Physical and C.H.N data of Schiff bases $[V]_n$.

Comp No.	Molecular Formula	Yields %	Color	M.P ^{0}C	Theoritical			Calc.		
					C%	H%	N%	C%	H%	N%
$[V]_2$	$C_{34}H_{28}N_6S_4O_4$	80	Pale yallow	210						
$[V]_3$	$C_{35}H_{30}N_6S_4O_4$	82	yallow	175	57.85	4.132	11.57	57.82	4.05	11.82
$[V]_4$	$C_{36}H_{32}N_6S_4O_4$	85	yallow	202						
$[V]_{10}$	$C_{42}H_{44}N_6S_4O_4$	80	Pale yallow	198	61.16	5.33	10.19	61.25	5.68	10.49
$[V]_{12}$	$C_{44}H_{48}N_6S_4O_4$	84	Pale yallow	184-186	61.97	5.63	9.85	61.88	5.85	9.96

Table (2): FTIR data of Schiff bases $[V]_n$

Comp No.	Characteristic bands FTIR spectra (cm^{-1})				
	νN-H	νC-H aliph.	νC=O amide	νC=N imine	νC-O ether
$[V]_2$	3211	2883-2932	1662	1614	1244
$[V]_3$	3210	2885-2930	1660	1614	1242
$[V]_4$	3210	2882-2932	1662	1614	1242
$[V]_{10}$	3208	2885-2932	1662	1616	1242
$[V]_{12}$	3208	2885-2930	1660	1616	1244

Table (3): physical and C.H.N data of series $[VI]_n$

Comp. No.	Molecular Formula	Yield %	Color	M.P ^{0}C	Theoritical			Calc.		
					C%	H%	N%	C%	H %	N%
$[VI]_2$	$C_{38}H_{32}N_6S_6O_6$	70	Yallow-orange	188-190	53.02	3.72	9.76	53.24	3.66	9.82
$[VI]_3$	$C_{39}H_{32}N_6S_6O_6$	75	yallow	165						
$[VI]_4$	$C_{40}H_{36}N_6S_6O_6$	82	orange	176	54.05	4.05	9.45	54.14	4.45	9.89
$[VI]_{10}$	$C_{46}H_{48}N_6S_6O_6$	85	yallow	154-156						
$[VI]_{12}$	$C_{48}H_{52}N_6S_6O_6$	86	Yallow-orange	149	57.6	5.2	8.4	57.84	5.45	8.69

Table(4): FTIR data of series $[VI]_n$

Comp No.	Characteristic bands FTIR spectra (cm^{-1})				
	νN-H	νC-H aliph.	νC=O ketone	νC=O amide	νC-O ether
$[VI]_2$	3140	2885-2962	1730	1664	1236
$[VI]_3$	3138	2890-2964	1730	1662	1236
$[VI]_4$	3145	2888-2964	1730	1664	1236
$[VI]_{10}$	3142	2885-2960	1730	1662	1232
$[VI]_{12}$	3140	2886-2966	1730	1662	1232

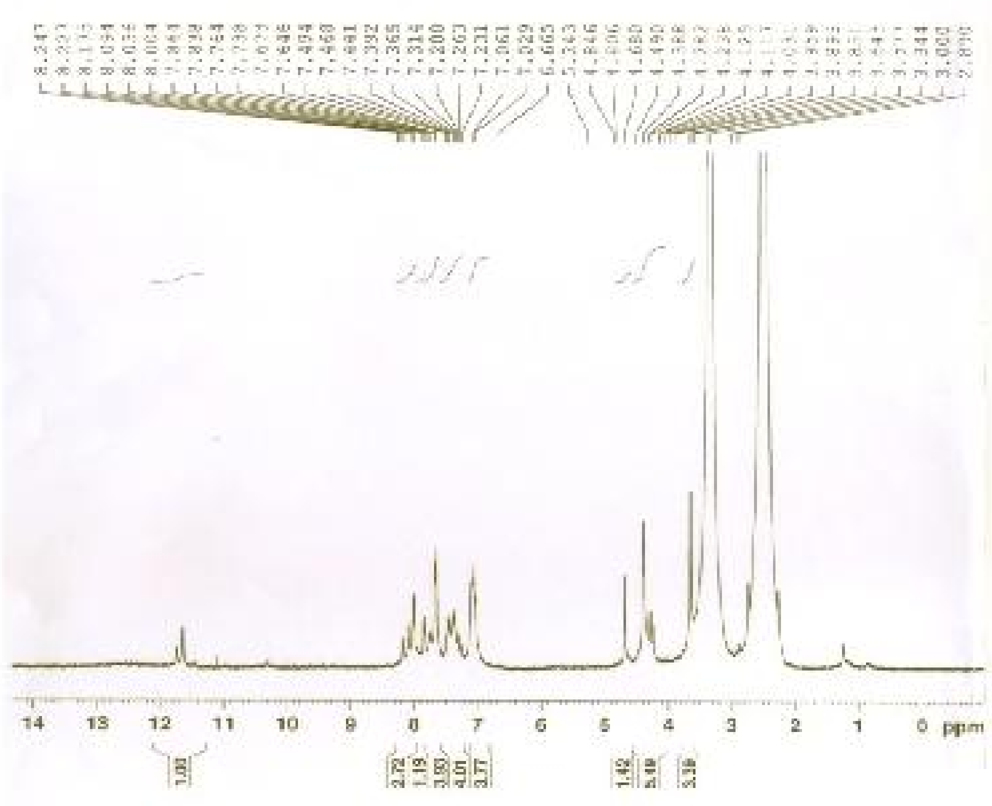

Fig.(1): ^{1}HNMR spectrum of compound $[VI]_2$

تحضير قواعد شف ومشتقات 2 , 3 -ثنائية التعويض- 1,3- ثايازولدين-4-ون جديدة تحتوي على وحدة البنزوثايازول

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الخلاصة

تم في هذا البحث تحضير سلسلتين جديدة من قواعد شف ومشتقات2 ,3- ثنائية التعويض-3,1-ثايازولدين-4-ون . ان تفاعل المركب 2- مركبتوبنزوثايازول مع الفا- كلورو حامض الخليك يعطي المركب [I] الذي تم تحويله الى الاستر المقابل [II] باستعمال الميثانول المطلق وبوجود حامض الكبريتيك المركز . حضر حامض الهيدرازيد [III] من تكثيف الاستر المحضر مع الهيدرازين المائي ومن ثم مفاعلة حامض الهيدرازيد الناتج مع الالديهيدات الثنائية $[IV]_n$ بوجود قطرات عديدة من حامض الخليك الثلجي لنحصل على قواعد شف جديدة $[V]_n$. اما مشتقات 1 , 3 - ثايازولدين-4- ون $[VI]_n$ فنحصل عليها من اضافة 2- مركبتو حامض الخليك الى مجموعة الازوميثين .

اثبت التركيب الكيميائي لهذه المركبات المحضرة باستعمال د رجات الانصهار، والاشعة تحت الحمراء FTIR، وطيف الرنين النووي المغناطيسي ^{1}HNMR لبعض منها .

الكلمات المفتاحية :بنزوثايازول , ثايازولدينون