

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

J. H. Tomma

Department of Chemistry , College of Education Ibn Al- Haitham  
University of Baghdad

Received in : 21 January 2008

Accepted in : 16 June 2011

## Abstract

Two series of Schiff Bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives were synthesized . Reaction of 2-mercaptobenzothiazole with  $\alpha$ -chloro acetic acid gave compound [I]. Esterification of carboxylic moiety 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 hydrazide 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  $^1H$ NMR (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-inflammatory [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  $500\text{-}4000\text{cm}^{-1}$  were obtained by using potassium bromide discs on FTIR instrument Model 8000 Shimadzu Spectrophotometer, Japan.  $^1\text{H}$ NMR 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  $[\text{V}]_n$  and  $[\text{VI}]_n$  are outlined in Scheme 1.

### 2-Mercapto acetic acid benzothiazole [I]

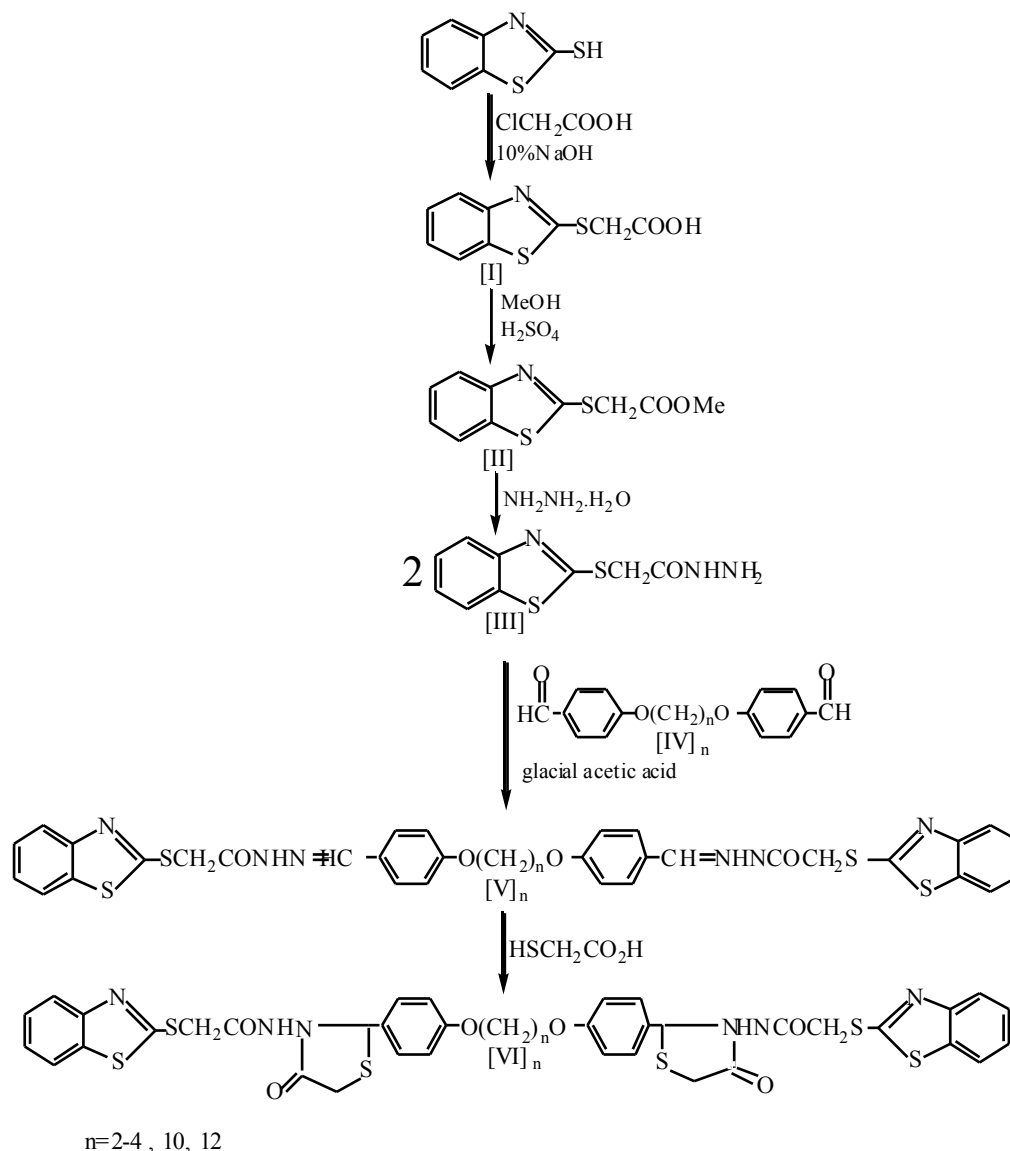
To a stirred mixture of  $\alpha$ -chloro acetic acid (0.01mol) and 10% aqueous sodium hydroxide (10 mL), a solution of 2-mercaptobenzothiazole (0.01mol) in 10% aqueous solution of sodium hydroxide (10 mL) was added. The mixture was refluxed for three hours. After cooling, the solution was acidified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

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- $\alpha,\omega$ -bis-4-oxybenzaldehyde [IV]<sub>n</sub>

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  $\alpha,\omega$ -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  $5^\circ\text{C}$  overnight, and then filtered, washed well with water, dried in air, recrystallized from ethanol(15), yield 88-98%.



Scheme 1

### $\alpha,\omega$ -bis-[(2-thioacetylhydrazidebenzothiazole-2-yl)benzylidene-4-oxyl]alkane [V]<sub>n</sub>

A mixture of compound [III] (0.02mmol), dialdehyde [VI]<sub>n=2</sub> (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]<sub>n</sub> with different n=3,4,10,12). Characterization data are presented in table 1. Polymethylene- $\alpha,\omega$ -bis-[N-(2-thioacetylhydrazinebenzothiazole)-4-oxo-1,3-thiazolidin-2-(p-oxybenzene)] [VI]<sub>n</sub>

A mixture of Schiff base [v]<sub>n</sub> (0.01mmol), thioglycolic acid (0.022mmol) was refluxed in dry benzene 6mL for 6 hours. The solvent was evaporated and the reaction mixture was

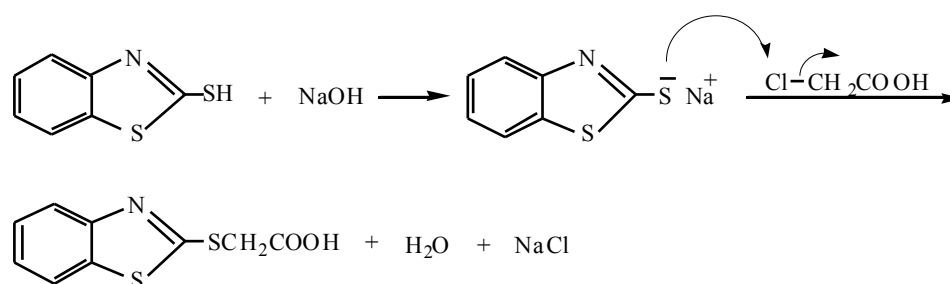
neutralized with cold dilute sodium bicarbonate solution , the formed product was filtered off and recrystallized from acetone to yield 70% , m.p=188-190 °C.

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

### Results and Discussion

The reaction between 2-mercaptobenzothiazole and  $\alpha$ -chloroacetic acid in alkali media was used to prepare the compound [I]. The  $\alpha$ -halogroup in  $\alpha$ -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  $\alpha$ -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).



Scheme 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<sup>-1</sup> due to  $\nu$ O-H group , sharp peak at 1690 cm<sup>-1</sup> assigned to carbonyl group of carboxylic moiety and the aliphatic C-H stretching at 2950 cm<sup>-1</sup> . also showed significant bands in the region (3060 , 1575 , 1454 and 750) cm<sup>-1</sup> that indicated the presence of benzothiazole moiety . 2-(Methylthioacetate) benzothiazole[II] was obtained by esterification of the carboxylic acid moiety of compound [I] using absolute methanol with conc. H<sub>2</sub>SO<sub>4</sub> was identified by FTIR spectrum . FTIR spectrum showed disappearance of two peaks of  $\nu$ OH and  $\nu$ C=O of carboxylic moiety of compound [I] together with the appearance of good peak at 1705 cm<sup>-1</sup> which could be attributed to  $\nu$ C=O of ester group .

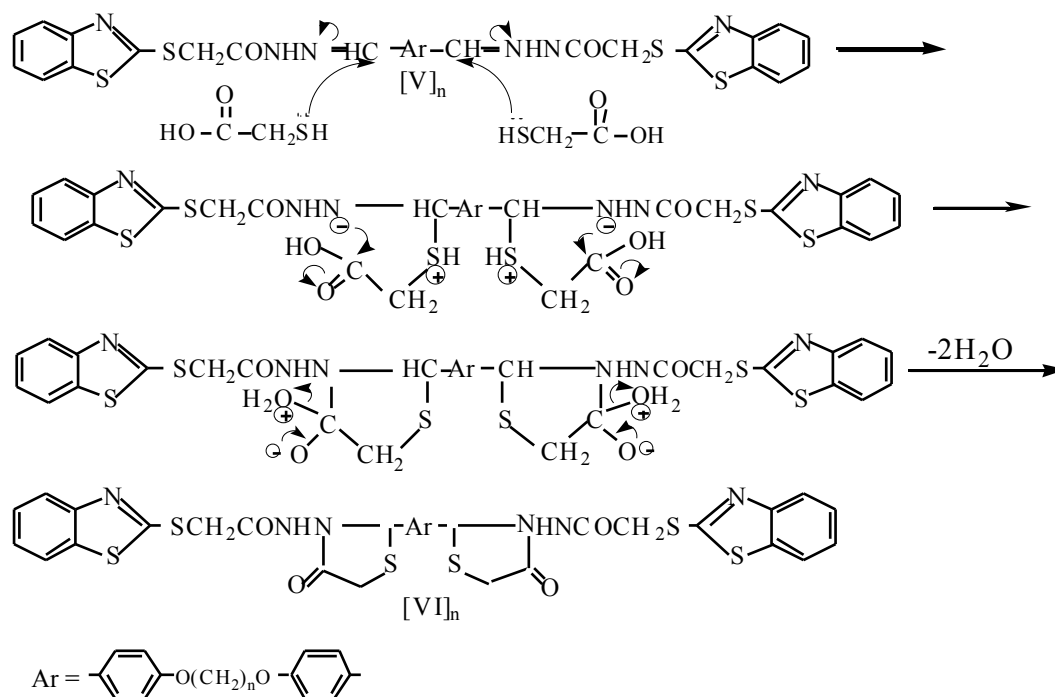
Condensation of ester [II] with hydrazine hydrate yielded the 2-(thioacetyl hydrazide)benzothiazole [III] which is characterized by its melting points 120°C . FTIR spectra , showed the following absorption bands:  $\nu$ C=O of amide group at 1645 cm<sup>-1</sup> , bands in the regions (3460, 3282, 3197) cm<sup>-1</sup> due to asymmetric and symmetric stretching vibration of NH , NH<sub>2</sub> groups , respectively. The spectra showed band at 2928 cm<sup>-1</sup> 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  $\alpha,\omega$ -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  $^1H$ NMR 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

$^1H$ NMR spectrum of compound  $[V]_{n=2}$  (DMSO as a solvent) showed single broad peak at  $\delta 9.15$  ppm that could be attributed to the two protons of  $NH$ , a multiplet signal at  $\delta 7.0-7.55$  ppm for eight aromatic protons of the phenyl rings of benzothiazole moiety and a doublet of doublets at  $\delta 7.8-8.25$  ppm for eight aromatic protons of two benzene rings. The imine protons appeared at  $\delta 4.92$  ppm. The  $^1H$ NMR spectrum also showed the a singlet at  $\delta 4.65$  ppm assigned for four protons of the mercapto methylene groups to  $(SCH_2)$  and triplet signal between  $\delta 3.80-3.92$  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 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  $^1\text{H}$ NMR spectroscopy . The FTIR exhibited significant bands at  $3210\text{ cm}^{-1}$  and  $1730\text{ cm}^{-1}$  which could be attributed to NH stretching and C=O stretching of thiazolidinone ring , respectively . Besides this , a band about  $1660\text{ cm}^{-1}$  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.

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

## References

- 1- El-Masry ,A. H.; Fahmy ,H. H. and Ali Abdalwahed, S. H. (2000) “ Synthesis and Antimicrobial Activity of Some New Benzimidazole Derivatives ”, *Molecules* 5:1429-1438 .
- 2- Kohli ,P.; Srivastava ,S. D. and Srivastava ,S. K. (2007) “ Synthesis and Biological Activity of Mercaptobenzimidazole Based Thiazolidinons and their Acrylidenes” *J. of the Chinese Chemical Society* , 54 :1003-1010.
- 3- Abod Elhafez ,O. M.; El Kharsy ,E. A.; Badria ,F. and Fathy, A. E. (2003) “ Synthesis and Biological Investigation of New Thiazolidinone and Oxadiazoline Coumarin Derivatives” ,*Arch Pharm Res.* , 26(8):686-696.
- 4- Vazzana , I.E. ;Terranova , F.; Mattioli and F. Sparatore (2004) “ Aromatic Schiff Bases and 2,3-Disubstituted 1,3-Thiazolidin-4-one Derivatives as Anti-inflammatory agents” ,*ARKIVOC* , V , 364-374.
- 5- Ling Liu ,H.; Li ,Z. and Anthonsen ,T. (2000) “ Synthesis and Fungicidal Activity 2-Imino-3(4-Arylthiazole-2-yl) Thiazoliden-4-ones and their Acrylidene Derivatives” ,*Molecules*, 5 :1055-1061.
- 6- Pareek,D. ; Chaudhary , M.; Pareek , P. K. ; Kant, R.; Ojha , K. G. ; Pareeka, R. and Pareeka, A. (2011) “ Synthesis and biological evaluation of 4-thiazolidinone derivatives incorporating benzothiazole moiety”, *Der Pharmacia Sinica* , 2(1): 170-181 .
- 7- Brown ,F. C. (1961) “ Thiazolidin-4-ones” . *Chem. Revs.* 61 :463-521.
- 8- Newcome, G. R. and Nayak, A. (1961), “Thiazolidin-4-ones ”. *adv. Heterocycl. Chem.* 25 : 83-112.
- 9- Ali , E. ; Tomma , J. and Mubbrik, S. (2008) “ Synthesis of Study The Biological Activity of Some Schiff-Bases Derived from 2-Aminobenzothiazole and Vanillin Derivatives ” , *Ibn Al-Haitham Journal for Pure and Applied Sciences* , 21(1):73-80.
- 10- Argyropoulou , I. ; Geronikaki, A.; Vicini,b. P. and Zanib, F. (2009) “Synthesis and biological evaluation of sulfonamide thiazole and benzothiazole derivatives as antimicrobial agents ” , *ARKIVOC* , (vi) :89-102.
- 11- Kaur, H.; Kumar, S. I. ; Singh, K.K. ;Saxena, A. and Kumar ,(2010), “Synthesis, Characterization and Biological Activity of Various Substituted Benzothiazole Derivatives” *Digest Journal of Nanomaterials and Biostructures* , 5(1): 67 - 76
- 12- Tomma, J. H.; Rouil, I. H. and AL-Dujaili ,A. H. (2009) “ Synthesis and Mesomorphic Behavior of Some Novel Compounds Containing 1,3,4-Thiadiazole and 1,2,4-triazole Rings ” , *Mol. Cryst. Liq. Cryst.* , 501 :3-19.

- 13- Vogel , I. (1974) “A text Book Of Practical Organic Chemistry” , Longman Group Ltd., London 3<sup>rd</sup> Ed.m , 781.
- 14- Smith, P. A. (1946) “ Organic Reactions” 3(9) : 366.
- 15- Griffin , A. and Havens, S. (1981) “ Mesogenic Polymers . III . Thermal Properties and Synthesis of Three Homologus Series of Thermotropic Liquid Crystalline “Backbone”Polyesters” , J. of Polym. Sci. Polymer Physics Edition , 19: 951-969.
- 16- Tomma , J. H. (2010) “ Synthesis , Characterization and Study The Liquid Crystalline Properties of N-Acyl , Thiourea and Imidazole Derivatives” , Ibn Al-Haitham J. for Pure and Appl. Sci., 23(3):134-151.
- 17- March, J. (1992) “Advanced Organic Chemistry Reaction Mechanism and Structure” , 4<sup>th</sup>. Ed., Wiley and Sons. Inc. New-York .

**Table (1): Physical and C.H.N data of Schiff bases [V]<sub>n</sub>.**

Comp No.	Molecular Formula	Yields %	Color	M.P °C	Theoretical			Calc.		
					C%	H%	N%	C%	H%	N%
[V] <sub>2</sub>	C <sub>34</sub> H <sub>28</sub> N <sub>6</sub> S <sub>4</sub> O <sub>4</sub>	80	Pale yellow	210						
[V] <sub>3</sub>	C <sub>35</sub> H <sub>30</sub> N <sub>6</sub> S <sub>4</sub> O <sub>4</sub>	82	yellow	175	57.85	4.132	11.57	57.82	4.05	11.82
[V] <sub>4</sub>	C <sub>36</sub> H <sub>32</sub> N <sub>6</sub> S <sub>4</sub> O <sub>4</sub>	85	yellow	202						
[V] <sub>10</sub>	C <sub>42</sub> H <sub>44</sub> N <sub>6</sub> S <sub>4</sub> O <sub>4</sub>	80	Pale yellow	198	61.16	5.33	10.19	61.25	5.68	10.49
[V] <sub>12</sub>	C <sub>44</sub> H <sub>48</sub> N <sub>6</sub> S <sub>4</sub> O <sub>4</sub>	84	Pale yellow	184-186	61.97	5.63	9.85	61.88	5.85	9.96



**Table (2): FTIR data of Schiff bases [V]<sub>n</sub>**

Comp No.	Characteristic bands FTIR spectra (cm <sup>-1</sup> )				
	νN-H	νC-H aliph.	νC=O amide	νC=N imine	νC-O ether
[V] <sub>2</sub>	3211	2883-2932	1662	1614	1244
[V] <sub>3</sub>	3210	2885-2930	1660	1614	1242
[V] <sub>4</sub>	3210	2882-2932	1662	1614	1242
[V] <sub>10</sub>	3208	2885-2932	1662	1616	1242
[V] <sub>12</sub>	3208	2885-2930	1660	1616	1244

**Table (3): physical and C.H.N data of series [VI]<sub>n</sub>**

Comp. No.	Molecular Formula	Yield %	Color	M.P °C	Theoretical			Calc.		
					C%	H%	N%	C%	H%	N%
[VI] <sub>2</sub>	C <sub>38</sub> H <sub>32</sub> N <sub>6</sub> S <sub>6</sub> O <sub>6</sub>	70	Yellow-orange	188-190	53.02	3.72	9.76	53.24	3.66	9.82
[VI] <sub>3</sub>	C <sub>39</sub> H <sub>32</sub> N <sub>6</sub> S <sub>6</sub> O <sub>6</sub>	75	yellow	165						
[VI] <sub>4</sub>	C <sub>40</sub> H <sub>36</sub> N <sub>6</sub> S <sub>6</sub> O <sub>6</sub>	82	orange	176	54.05	4.05	9.45	54.14	4.45	9.89
[VI] <sub>10</sub>	C <sub>46</sub> H <sub>48</sub> N <sub>6</sub> S <sub>6</sub> O <sub>6</sub>	85	yellow	154-156						
[VI] <sub>12</sub>	C <sub>48</sub> H <sub>52</sub> N <sub>6</sub> S <sub>6</sub> O <sub>6</sub>	86	Yellow-orange	149	57.6	5.2	8.4	57.84	5.45	8.69

**Table( 4): FTIR data of series [VI]<sub>n</sub>**

Comp No.	Characteristic bands FTIR spectra (cm <sup>-1</sup> )				
	νN-H	νC-H aliph.	νC=O ketone	νC=O amide	νC-O ether
[VI] <sub>2</sub>	3140	2885-2962	1730	1664	1236
[VI] <sub>3</sub>	3138	2890-2964	1730	1662	1236
[VI] <sub>4</sub>	3145	2888-2964	1730	1664	1236
[VI] <sub>10</sub>	3142	2885-2960	1730	1662	1232
[VI] <sub>12</sub>	3140	2886-2966	1730	1662	1232

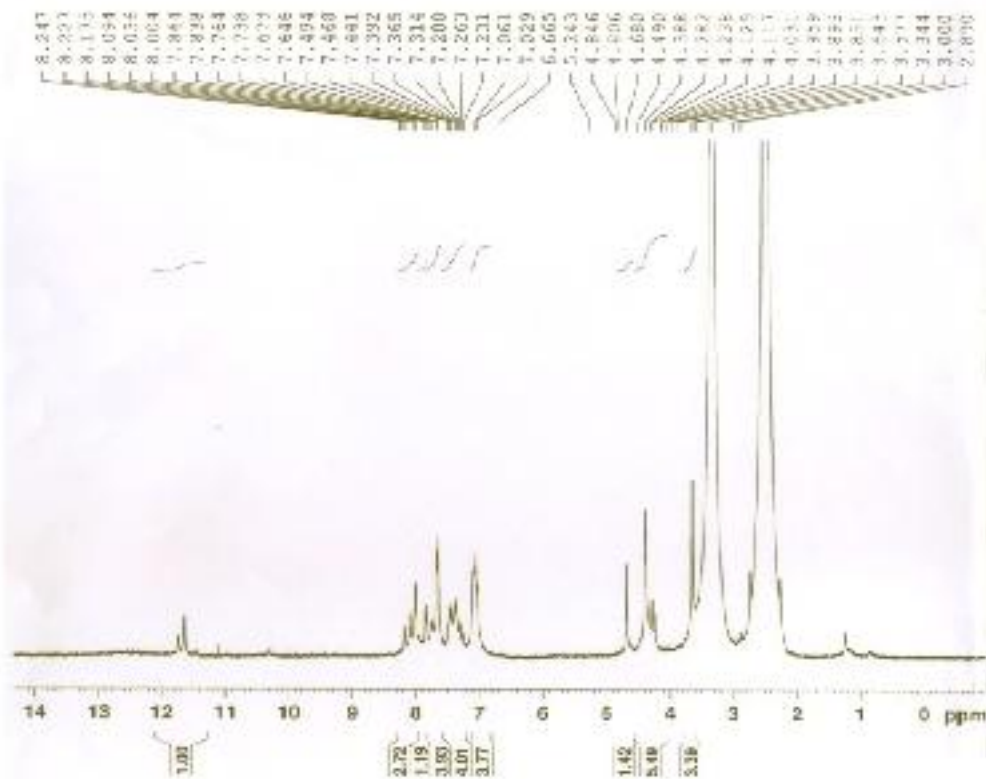


Fig.(1): <sup>1</sup>H NMR spectrum of compound [VI]<sub>2</sub>

## تحضير قواعد شف ومشتقات 2 , 3 -ثنائية التعويض - 1,3- ثيازولدين-4-

## ون جديدة تحتوي على وحدة البنزو ثيازول

جمبد هرمز توما

قسم الكيمياء، كلية التربية - ابن الهيثم ، جامعة بغداد

استلم البحث في : 21 كانون الثاني 2008

قبل البحث في : 16 حزيران 2011

## الخلاصة

تم في هذا البحث تحضير سلسلتين جديدة من قواعد شف ومشتقات 2, 3- ثنائية التعويض-1,3-ثيازولدين-4-ون . ان تفاعل المركب 2- مركبتوبنزوثيازول 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]<sub>n</sub> بوجود قطرات عديدة من حامض الخليك الثلجي لنحصل على قواعد شف جديدة [V]<sub>n</sub> . اما مشتقات 1 , 3 - ثيازولدين-4-ون [VI]<sub>n</sub> فنحصل عليها من اضافة 2- مركبتو حامض الخليك الى مجموعة الازوميثين .

اثبت التركيب الكيميائي لهذه المركبات المحضرة باستعمال درجات الانصهار، والاشعة تحت الحمراء FTIR،

وطيف الرنين النووي المغناطيسي <sup>1</sup>HNMR لبعض منها .

الكلمات المفتاحية: بنزو ثيازول , ثيازولدينون