Synthesis and Characterization of Some New 1,2,3-Triazole, Pyrazolin-5-one and thiazolidinone Derivatives

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Abstract

Five membered heterocyclics derivatives were synthesized in this work by three routes. The first route includes the synthesis of N-benzoic acid 1,2,3,-triazole derivatives (3),(4) by diazotation of methyl-2-amino benzoate and treating the resulted salt (1) with sodium azide and ethyl acetoacetate or acetyl acetone, respectively. In the second route, derivatives of pyrazole (8) pyrazolin-5-one (9), (10) were prepared by the reaction of the salt (1) with some active methylene compounds to give the corresponding hydrazones derivatives (5-7) which then they were treated with hydrazine hydrate. The third route afforded the synthesis of three derivatives (12), (15a), (15b) of thiazolidinone by two different methods. AII compounds were confirmed by their melting points, *FTIR, U.V*-vis spectra and ^{1} *H-NMR* spectra for some of them.

Keywords: 1,2,3- Triazole, pyrazolin-5-one, Schiff bases, thiazolidinone.

Introduction

Organic compounds containing five membered heterocyclic ring like; 1, 2, 3-triazole, pyrazole and thiazolidinone have occupied unique place in the field of medicinal chemistry due to their diverse biological activities such as: antifungal [1], antimicrobial [2,3,4], antiflammatory [5,6], cytotoxicity [7], antioxidant [8], antihistaminic [9], antituberculor [10] and anticonvulsant [11]. Recently it was found that 1,2,3-triazoles could be used as a peptide surrogates in the rapid synthesis of HIV-1 protease inhibitors [12] and as cis peptide bond surrogate in protein prosthesis [13].It was found that pyrazole and 4-thiazolidinone derivatives have additional industrial applications [14], [15].

Experimental

General:

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The *FTIR* spectra (KBr discs) were recorded with a Pye-Unicam SP3-100 or Shimadzu FTIR-8400.UV spectra were recorded on a Shimadzu 160A UV/VIS spectrophotometer using absolute ethanol as solvent. ^{1}HNMR spectra were recorded on a make Bruker model ultrashield 300 MHz NMR at Al-Albyt University, Jordan DMSO-d^{6} was used as solvent and TMS as an internal reference. All chemical were obtained from Fluka or BDH.

Diazotization of methyl-2amino benzoate (1).

A solution of methyl-2-amino benzoate (0.01 mole, 1.3 mL) in concentrated HCl (3mL) was cooled to 0-5 ^{o}C , a cooled solution of sodium nitrite (1.5 g in 10 mL of water) was added dropwise during 10 minutes, then The reaction mixture was stirred for 30 minutes.

Preparation of methyl 2-Azidobenzoate (2)

(2.5mL) of an aqueous solution of sodium azide (0.012 mole, 0.78g) was added dropwise to an aqueous solution of diazonium salt (**1**). The mixture was stirred for further 20 minutes to give an oily compound (**2**).

Preparation of 1-(4-Carboxyphenyl)-5-methyl- 1H-1,2,3-triazole-2-carboxylic acid (3) [16].

To a cold solution of sodium ethoxide (7 mL) and ethyl acetoacetate (0.01 mole, 1.3 g), methyl-2-azidobenzoate (2) (0.01 mole, 1.3 mL) was cautiously added and the mixture was heated under reflux on a water bath for 3 hrs. The resulting solid was separated and recrystallized from ethanol.

Preparation of 1-(4-acetyl-phenyl)-5-methyl-1H-1,2,3 triazole -2-Carboxylic acid (4)

A mixture of methyl-2-azidobenzoate (0.01 mole, 1.3 mL) and acetyl acetone (0.01 mole, 1.03 mL) in methanol (30 mL) was cooled to 0^{o}C. Sodium methoxide (0.01 mole) in methanol (20 mL) was added

gradually to the mixture and heated under reflux on a water bath for 6 hours. The crude product was recrystallized from ethanol.

General procedure for the preparation of hydrazono derivatives (5-7) [17].

To an ice- cold mixture of some active methylene compounds like acetyl acetone, ethyl cyano acetate or ethyl acetoacetate (0.01 mole) and sodium acetate (0.05 mole, 4.1 g) in ethanol (30 mL). A solution of diazonium salt compound (1) (0.01 mole) was added dropwise with stirring over 15 minutes. After wards the stirring was continued for 30 minutes and the reaction mixture then left for 2 hours at room temperature. The solid product was collected and recrystallized from ethanol to give the corresponding hydrazono derivatives (5-7).

General procedure for the Cyclization Reactions of hydrazono derivatives with Hydrazine Hydrate to give. 2-((3-5-dimethyl-1H –Pyrazol-4-yl)diazenyl) benzohydrazide (8),2-((3-amino-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl) benzohydrazide (9) and 2-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol -4-yl)diazenyl) benzohydrazide (10).

A mixture of compounds (5-7) (0.01 mole) and hydrazine hydrate (3 mL) in ethanol (20 mL) was heated under reflux for 4-6 hrs. The solvent was concentrated and the reaction product was allowed to cool. The separated product was filtered off, washed with water, dried and recrystallized from ethanol.

Preparation of methyl (2-(3-phenyl thioureido) benzoate (11).

A mixture of methyl-2-amino benzoate (0.01 mole ,1.3 mL) and phenyl isothiocyanate (0.01 mole, 1.2 mL) in absolute ethanol (20 mL) was refluxed for 3hrs and cooled. The solid product was filtered and recrystallized from ethanol.

Preparation of 3-phenyl- 1,3- thiazolidine -2,4- dione-2-(methyl benzoate-2-yl-hydrazone) (12).

Ethyl chloro acetate (0.01 mole, 1.06 mL) was added dropwise to a stirred solution of compound (11) (0.01 mole, 2.8 g) and anhydrous sodium acetate (0.01 mole) in (20 mL) absolute ethanol. The reaction mixture was refluxed for 6 hrs. The solid product was filtered and recrystallized from ethanol.

Preparation of 2-amino benzhydrazide. (13).

A mixture of methy 2-amino benzoate (0.01 mole) and hydrazine hydrate 60% (10 mL) in ethanol (30 mL) was heated under reflux for 4hr. The reaction mixture was concentrated and cooled. The solid was filtered, washed with water and recrystallized from ethanol.

General procedure for preparation of Schiff bases(14_a)and (14_b).

A mixture of compound (13) (0.002 mole, 0.3 gm) and substituted aromatic aldehyde (o-chloro benzaldehyde or 5-chloro salicylaldehyd) (0.002 mole) in ethanol absolute (20 mL) was refluxed for 1hr and cooled. The solid product was filtered and recrystallized from ethanol.

General procedure for preparation of thiazolidenon derivatives (15_a)and (15_b)

A mixture of Schiff bases (14a,b) (0,002 mole) and mercapto acetic acid (0.04 mole, 0.26ml) in dry benzene (30 mL) was refluxed for 10hrs .The mixture was concentrated and recrystallized from methanol.

All physical properties for prepared compounds and Infrared data were reported in Table (1).

Table (1)
Physical properties of the prepared compounds.

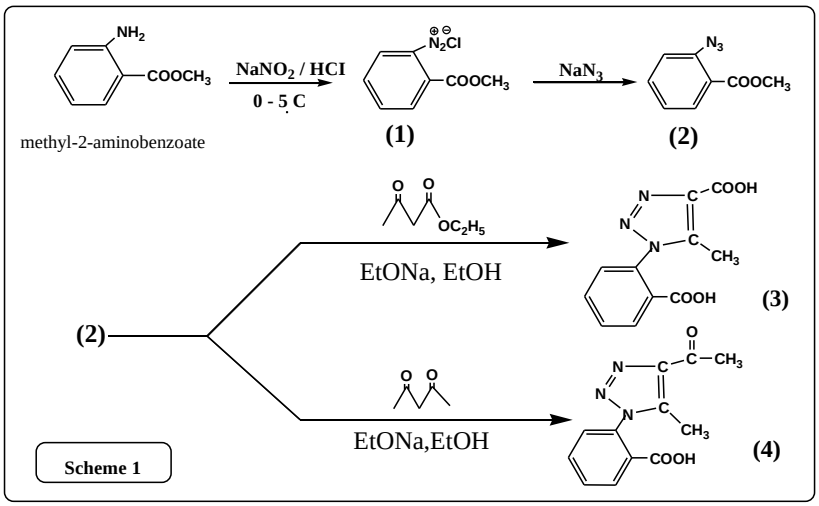
com No.	*Formula*	*MP. ^0C*	*Yield%*	*Colour*	*UV, λ_{max}*	*Infrared data(V,cm^{-1}) (KBr disc)*
2	$C_8H_7N_3O_2$	Oily	79	Pale Brawn	293 261	3001(C-H_{ar}),2954(C-H_{al}) 2121(N=N-$N_{azid\ asym}$), 1728(C=O_{est})
3	$C_{11}H_9N_3O_4$	208-210	64	Brown	267 215	(3300-2500)(O-H), 3008(C-H_{ar}) 2954 (C-H_{al}),1700 (C=O),1002(N=N-N $_{ring}$)
4	$C_{12}H_{11}N_3O_3$	234-236	55	Brown	303 224	3300-2500(O-H) ,3001(C-H_{ar}), 2950 (C-H_{al}),1710(C=O_{ket}), 1690(C=O_{acid}), 949(N-N=N $_{ring}$)
5	$C_{13}H_{14}N_2O_4$	138-140	83	Yellow	244 354	3176(NH),3070(C-H_{ar}),2959(C-H_{al}) 1730-1670(C=O),1640(C=N)
6	$C_{13}H_{13}N_3O_4$	142-144	75	Deep yellow	346 290	3137 (NH),3004(C H_{ar}),2997(C-H_{al}), 2222(CN) ,1704(C=O_{ester})
7	$C_{14}H_{16}N_2O_5$	157-159	80	Yellow	267 238	3271 (NH),3004(C-H_{ar}),2972(C-H_{al}), 1643(C=N) ,1735-1700(C=O)
8	$C_{12}H_{14}N_6O$	125-130	61	Red	290 324	3348,3157(NH.NH_2) , 1680(C=O_{amid}) ,1508(N=N)
9	$C_{10}H_{10}N_7O_2$	176-178	68	Orange	287 313	3534,3517(NH_2) 3290,3168(NH.NH_2), 1643 (C=O_{amid}), 1519(N=N),
10	$C_{11}H_{12}N_6O_2$	185-187	60	Orange Yellow	253 298	3280,3135(NH.NH_2) ,1690 (C=O_{amid}) ,1480(N=N)
11	$C_{15}H_{14}N_2O_2S$	>280	74	White	327	3247,3150(NH.) ,3030(C-H_{ar}) , 1666(C=O_{amid})1265(C=S)
12	$C_{17}H_{14}N_2O_3S$	102-104	57	White	275 325	3062(C-H_{ar}) ,2985(C-H_{al}) , 1735(C=O_{ester}) ,1689(C=O_{amid}), 1628 (C=N) , 694(C-S)
13	$C_7H_9N_3O$	121-123	76	Off-White	279 367	3445(NH_2) ,3325,3120 (NH.NH_2) ,1620(C=O_{amid})
14a	$C_{14}H_{12}N_3OCl$	195-198	83	Pale Yellow	301	3421,3327(NH_2) ,3219(NH), 3034(C-H_{ar}) ,1650(C=O_{amid}) , 1639(C=N) ,1046(C-Cl)
14b	$C_{14}H_{12}N_3O_2Cl$	215-217	80	Yellow	259 332	3483(O-H) ,3377(NH_2) ,3041 (C-Har), 1643(C=O) ,1612 (C=N),1308(C-O_{phe})
15a	$C_{16}H_{14}N_3O_2SCl$	143-146	65	Greenish Yellow	287 316	3456-3243(NH_2) ,1668 (C=O_{amid}) , ,1014(C-Cl) ,684(C-S-C) 1734(C=O $_{of\ thaizolidinon\ ring}$)
15b	$c_{16}H_{14}N_3O_3SCl$	223-226	58	Pale Yellow	323 245	3475(O-H) ,3425-3275(N-H) , 1710(C=$O_{thaizolidinon\ ring}$) , 3049(C-$_{Har}$) ,1665(C=O_{amid})

Results and Discussion

In the present work the synthesis of some new 1,2,3-triazoles , pyrazole, pyrazolin-5-one and Thiazolidinon derivatives were achieved from methyl-2-amino benzoate.

1-(4-Carboxyphenyl)-5-methyl- 1H-1,2,3-triazole-2-carboxylic acid (3) and 1-(4-acetyl-phenyl)-5-methyl- 1H-1,2,3 triazol -2-Carboxylic acid (4) were Prepared by the reaction of methyl-2-azido benzoate (2) with

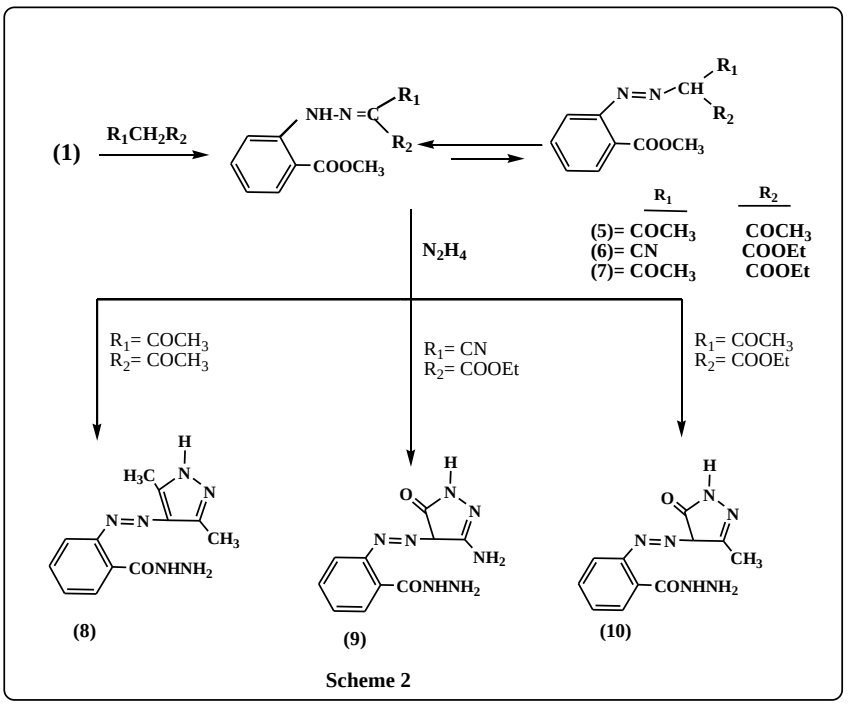
ethyl acetoacetate or acetylacetone in sodium ethoxid using absolute ethanol as a solvent (Scheme (1)).



The structure of compounds (3) and (4) were confirmed by physical properties which are listed in Table (1). *FTIR* spectra showed the disappearance of the azide group (N_3) band in the starting material (2) at (2121 cm^{-1}) which is a good indication for successful condensation [18]. The spectrum also shows absorption bands at (1700 cm^{-1}) referred to (C=O) stretching vibration of Carboxylic acid, (3300-2500cm^{-1}) due to (OH) and (1710 cm^{-1}) referred to (C=O) of the keton for compound (4). While the ^{1}H-NMR Spectra data of compound (3) shows (δ ppm in DMSO-d^6 solvent). 3.9 (s, 3H, CH_3); 7.2-8.6 (m, 4H, Ar-H) and singlet at 11.8 and 12.2 due to tow COOH proton.

The U.V .spectrum of this compound (4) was obtained in methanol exhibited the characteristic bands at (303 nm) responsible for (n-π*) transition and (224 nm) due to (π-π*) transition.

The diazonium chlorides (1) was synthesized by diazotization of methyl-2-amino benzoate using a mixture of sodium nitrite and HCl at 0-5 ^{0}C, The obtained diazonum salt was treated with calculated amounts of some active methylene compounds like acetylacetone , ethyl cyanoacetate or ethyl acetoacetate in ethanol in the presence of sodium acetate to afford the corresponding hydrazono derivatives (5-7) (Scheme (2)).



Compounds (5-7) were characterized by phesical propraties their m.p., UV and FTIR spectra and one of them were characterized by ^{1}H-NMR. For example the FTIR spectrum of (6) shows an absorption band at (2222 cm^{-1}) corresponding to the vibration of the (C N) and another band at (1704 cm^{-1}) characteristic of the carbonyl group of ester.

While the ^{1}H-NMR spectra of compound (6) shows, δ 1.35(t,3H,CH_3) ; 4.34 (q ,2H, OCH_2) ; 3.9 (s, 3H, $COCH_3$) ; 7.2- 8.0 (m ,4H, Ar-H) and 12 (s,H,NH).

Refluxing of compound **5** with hydrazine hydrate in ethanol for six hours afforded 2-((3,5-dimethyl-1H-pyrazol-4-yl) diazenyl) benzohydrazide (8). The *FTIR* Spectra of (8) showed the disappearance of characteristic bands of acetyl carbonyl group and carbonyl group of ester and the appearance of two strong bands at (3348-3157cm^{-1}) due to NH NH_2 and at (1580cm^{-1}) due to (N=N) group.

Hydrazono derivatives (6) and (7) cyclized with hydrazine hydrate in boiling ethanol were expected to lead to the formation of the corresponding pyrazolin-5-one derivatives (9) and (10).

Assignment of the structure of compound (9) was obtained by *FTIR* and ^{1}H-NMR The *FTIR* spectra of (9) was characterized by the disappearance of ν (CN) band and the appearance of a two band in the region (3534-3517 cm^{-1}) attributed to the stretching vibration of the NH_2 group, while the ^{1}H-NMR spectrum of (9) exhibited two singlet signals at 9.9 and at 10.4 attributed to the two NH groups and singlet at 5.8 and at 4.5 due to tow NH_2 proton and 7.1-8.1 (m,4H , Ar-H) Fig.(1) [14].

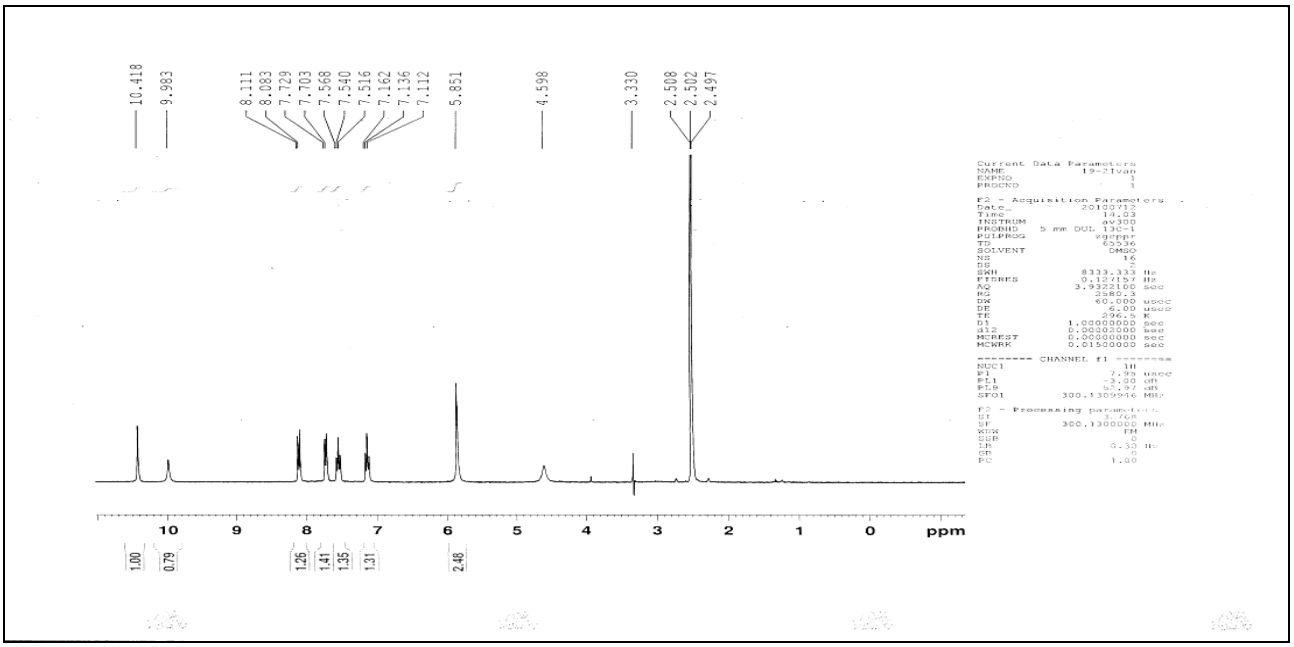
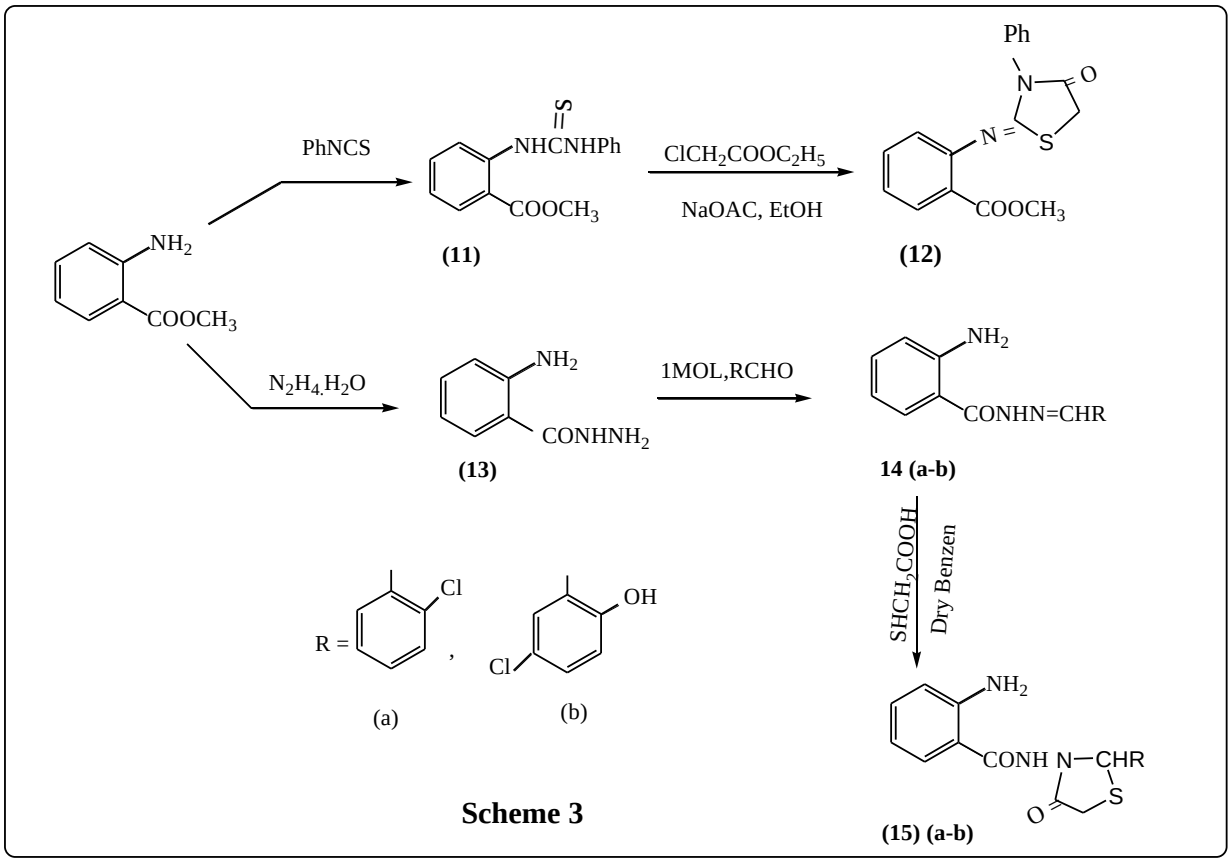


Fig. (1) ^{1}H-NMR Of the compound (9).

Reaction between methyl-2-aminobenzoate and phenyl isothiocyanate afforded the corresponding thiosemicarbazide derivatives (11) in moderate yield (Scheme (3)).



Scheme 3

The *FTIR* spectra of (11) display (C=S) stretching band at (1255cm$^{-1)}$) and (NH) stretching band at (3247cm^{-1}) .Refluxing of compound (11) with ethylchloroacetate and anhydrous sodium acetate in absolute ethanol for six hours afforded 4-thiazolidenone (12). The structure of(12) was confirmed by the presence of ($C=O_{amid}$) stretching band at (1689cm^{-1}) and (C=N) stretching band at (1628cm^{-1}) while the ^{1}H-NMR Spectra data of compound (12) shows δ ppm in DMSO-d^{6} solvent.1.22(s, 2H,CH_2); 3.9 (s ,3H ,CH_3); 7.4-8 (m, 9H, Ar-H).

On the other hand the reaction of methyl-2-aminobenzoate with hydrazine hydrate. Afforded 2-amino benzohydrazide (13), Condensation of (13) with aryl aldehydes in absolute ethanol gave the Schiff's bases (14a) and (14b).

Moreover, treatment of Schiff's bases the (14a) and (14b) with mercapto acetic acid in dry benzene gave the thiazolidenon derivatives (15a) and (15b) Structures of these compound were confirmed by the disappearance of (C=N)band at (1600-1649 cm^{-1}) and the appearance of the carbonyl band due to thiazolidinone ring at (1710-1745cm^{-1}) and the (C-S-C) band at 684 cm^{-1}.

References

[1] Shukla D. K., Sribastava S. D., "Synthesis of some new 5-[2-{(1,2,3-benzotriazole)-1-yl-methyl}-1-(4-substituted aryl-3-chloro-2-oxo azetidine)]-amino-1,3,4-thiadiazoles :Antifungal and antibacterial agents" *Indian Journal of Chemistry*, vol.47B March, pp.463-469, 2008.

[2] Saini R., Awani k. Rai, Shahar Yar M., "Synthesis and Biological Evaluation of 2,5 Di- substituted 1,3,4 oxadiazoles", *Asian J. Research Chem.* Vol. 2(1), pp. 34-36, 2009 .

[3] Ravikumar P., Shantayadav M., Srinivasa Rao "T. nthesis and Antimicrobial Activity of Some New Substituted Aryloxy-4-Thiazolidinones" *E-Journal of Chemistry*, vol. 3, No.10, pp 44-48, 2006.

[4] Mudasir Rashid & Abdul Rauf, "Substituted 1,2,4- triazoles and thiazolidinones from fatty acids :Spectral characterization and antimicrobial activity", *Indian Journal of Chemistry*, vol.48b, pp. 97- 102, 2009 .

[5] Arunkumar S., Ilango K. R.S. Manikandan, N. Ramalakshmi, "Synthesis and Anti- inflammatory Activity of Some Novel Pyrazole Derivatives of Gallic Acid", *E-Journal of Chemistry*, vol.6(S1), pp.123-128, 2009 .

[6] Trilok Chandra, Neha Garg and Ashok Kymar, 2009, "Synthesis of Sulpha Drug Quinazolin-4-one Derivatives and Their Evaluation for Anti-inflammatory Activity", World *Journal of Chemistry*, vol. 4(2), pp.210-218, 2009.

[7] Nusrat Binta Ahasan,. Rabiul Islam Md, 2007, "Cytotoxicity study of pyrazole derivatives", Bangladesh *J. Pharmacol*, vol.2, pp.81-87, 2007.

[8] Parameswaran M. A., Thenungal kochupappy and Gopalakrishnan subbuchettiar, "Synthesis of coumarin heterocyclic derivatives with antioxidant activity in vitro cytotoxic activity against tumour cells", *Acta pharm*., vol. 59, 159-170, 2009.

[9] Veerachamy Alagarsamy, Rajani Giridhar, and Mangae Ram, "Synthesis and H1-Antihistaminic Activity of Some Novel 1-Substituted -4-(3- methylphenyl)-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-ones", *Biol.pharm. Bull*., 28(8), 1531-1534, 2005.

[10] Parekh H. H., parikh K.A., Parikh A.R., "Synthesis of Some Thiazolidinone Derivatives as Antitubercular Agents", *Journal of Sciences, Islamic Republic of Iran*, vol.15 (2), pp.143-148, 2004.

[11] Aysel Gursoy, Nalan Terzioglu, "Synthesis and Isolation of New Regioisomeric 4- Thiazolidinones and Their Anticonvulsant Activity", *Turk.J. Chem*., 29, 247-254, 2005.

[12] Ashraf Brik, Jerry Al., Ying-Chuan Lin, John H. Elder, 1,2,3-Triazole as a peptide Surrogate in the Rapid Synthesis of HIV-1Protease Inhibitors "*ChemBioChem*, vol.6, 1167-1169, 2005.

[13] Annie Tam, Ulrich Arnold,Matthew B. and Ronald T. Raines ,"Protein Prosthesis : 1,5-Disubstituted –[1,2,3]-triazoles as cis-Peptide Bond Surrogates", *J.Am Chem. Soc*. , vol. 24, pp.12670-12671, 2007.

[14] Smokal V., "Synthesis polymerization ability, nonlinear optical properties of methacrylic monomers and polymers with benzylidene moiety", *Journal of chemistry and chemical technology*, vol. 1, No.3 , pp. 131-135, 2007.

[15] Srividhya D., S. Maniunathan and S. Thiriumaran, "Synthesis and characterize-ation of New Heterocyclic liquid crystals", *E-Journal of chemistry*, vol.6 No.3, pp. 928-937, 2009.

[16] Kolb H.C., One step synthesis of 1,2,3-triazole carboxylic acids, U.S Pat.6, 642, 390 B, 4 Nov. 2003 .

[17] Saleh M. A., Mohamed F. Abdel-Megeed and Mohamed A. Abdo, "Synthesis of novel 3H-Quinazolin-4-ones Containing Pyrazolinone, Pyrazole and Pyrimidinone Moieties", *Molecules*, vol.8, pp. 363-373, 2003.

[18] Phillip Crews J.R. and Jaspars, *"Organic Structure Analysis"* 2nd ed. Oxford university press, Inc. New York, pp. 546, 1998 .

الخلاصة

تم في هذا البحث تحضير سلسلة من المركبات الحلقية الخماسية غير المتجانسة من خلال ثلاث مسارات. يتضمن المسار الأول تحضير مشتقات حامض البنزويك ٣،٢،١- ترايازول المرقمة (٣) و (٤) من تحويل مثيل ٢- امينو بنزويت الى ملح الديازونيوم (١) ومن ثم مفاعلة الملح الناتج (١) مع صوديوم ازايد ومثيل اسيتو اسيتيت او اسيتايل اسيتون على التوالي . في المسار الثاني تم تحضيرمشتقات بايرزولين-٥- ون من تفاعل الملح المذكور (١) مع بعض مركبات المثيلين الفعالة للحصول على مشتقات هيدروزونو المقابلةالمرقمة(٥-٧) ومن ثم اضيف اليها هيدرازين هيدريت للحصول على المركبات (٨) و (٩) و (١٠). المسار الثالث يتضمن تحضير مشتقات ثايازوليدينون باستخدام طريقتين مختلفتين للحصول على المشتقات(١٢) و (١٥). شخصت المركبات المحضرة عن طريق قياس درجة الانصهار واطياف الاشعة تحت الحمراء ،والاشعة فوق البنفسجية ،والرنين النووي المغناطيسي لبعض منها.