

Conversion of Substituted Thiosemicarbazide and 1,3,4-Oxadiazole to 5- Substituted / 4,5- Di substituted -1,2,4-Triazole-3-thiol

Khalid M. Daoud

Shaima S. Ismaeel

Yaser S. Al-Jawharji

University of Mosul - College of Education

Received: 26/3/2007 ; Accepted: 4/6/2007

Abstract:

In this paper substituted 1,2,4-triazoles were synthesized from ethyl glycinate, the synthesis route pass through substituted thiosemicarbazides or 1,3,4-oxadiazoles. Ethyl glycinate prepared from glycine, which was treated with HCl gas in absolute ethanol to give ethyl glycinate hydrochloride, which then treated with dry ammonia in methylene chloride to give the free glycine ester. Treatment of ethyl glycinate with substituted benzaldehyde gave the corresponding Schiff base, which were converted to hydrazide by their reaction with hydrazine hydrate in ethanol. The hydrazides were treated with carbon disulfide in ethanolic potassium hydroxide to give substituted 1,3,4-oxadiazole. Treatment of the oxadiazoles with primary amines or hydrazine hydrate gave 3,4,5-trisubstituted 1,2,4-triazole. Hydrazides were converted to substituted thiosemicarbazides by their reaction with ammonium thiocyanate, which then treated with sodium hydroxide solution to give 3,5-disubstituted-1,2,4-triazole.

The structures of the synthesized compounds were established by physical and spectral methods.

تحويل الثايوسميكابازيدات المعوضة و ١.٣.٤ اوكسادايازول الى ٥-بدائل / ٤.٥ – ثنائية البدائل – ١.٣.٤ ترايازول-٣- ثايول

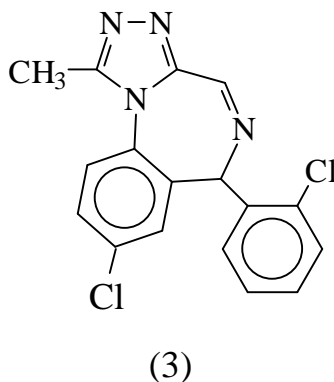
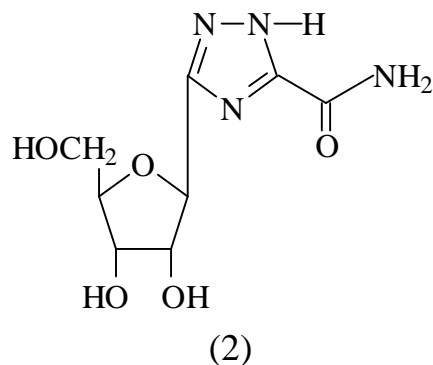
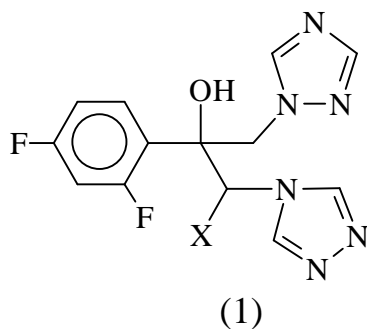
ا.م.د. خالد محمود داود
جامعة الموصل / كلية التربية

ملخص البحث :

تم في هذا البحث تحضير عدد من معوضات ٤،٢،١-ترايازول من كلايسينات الاثيل وذلك من خلال تكوين الثايوسميكابازيد او ٤،٣،١-اوكسادايازول. حضر كلايسينات الاثيل من الكلاسين حيث تم تفاعله مع غاز كلوريد الهيدروجين في الايثانول المطلق ليعطي ملح استر الكلاسين، واعطى تفاعل الملح المتكون مع غاز الامونيا الجافة في كلوريد الميثيلين، كلايسينات الاثيل، تم مفاعلة كلايسينات الاثيل مع معوضات البنزالديهايد لتعطي قواعد شيف المقابلة. حولت الاسترات الناتجة الى هيدرازيدات من خلال مفاعلتها مع الهيدرازين المائي في الايثانول. تم مفاعلة الهيدرازيدات مع ثنائي كبريتيد الكاربون في محلول هيدروكسيد البوتاسيوم الايثانولي ليعطي ٤،٣،١-اوكسادايازول المعوض. كما تم تحويل الاوكسادايازولات الى ٤،٢،١-ترايازول ٥،٤،٣-ثلاثي التعويض من خلال تفاعلها مع عدد من الامينات او الهيدرازين المائي. حولت الهيدرازيدات الى معوضات الثايوسميكابازيدات من خلال مفاعلتها مع ثايوسيانات الامونيوم والتي تم مفاعلتها مع محلول هيدروكسيد الصوديوم لتعطي ٥،٣-ثنائي التعويض ٤،٢،١- ترايازول. شخّصت المركبات المحضرة بالطرق الفيزيائية والطيفية.

Introduction :

The substituted 1,2,4-triazoles are five membered ring heterocyclic compounds, which draw the attention of the research workers due to their biological activities. It was found that compound (1) has antifungal properties⁽¹⁾, and compound (2) acts as anticancer agent⁽²⁾. Substituted 1,2,4-triazoles⁽³⁾ show activity against tuberculosis triazolam (3) used as hypotic drug⁽⁴⁾ and anti-inflammatory agent⁽⁵⁾.



In agricultural field some substituted 1,2,4-triazoles, show activity against⁽⁶⁾ aphids, or act as plant growth regulator⁽⁷⁾.

Substituted 1,2,4-triazoles were synthesized from substituted thiosemicarbazides by their reaction with sodium hydroxide solution⁽⁸⁾, 4-amino-3,5-diphenyl-1,2,4-triazole was synthesized by heating acid hydrazide to 200 °C⁽⁹⁾. Substituted thiosemicarbazide was treated with some esters in presence of sodium methoxide in methanol to give substituted 1,2,4-triazoles⁽¹⁰⁾. In the present work the synthesis of 1,2,4-triazoles from substituted thiosemicarbazides or from substituted oxadiazoles is reported.

EXPERIMENTAL

All chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany,

using KBr discs. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using chloroform as a solvent.

Ethyl glycinate hydrochloride (1)⁽¹¹⁾

Dry HCl gas was passed through a solution of glycine (7.5 g, 0.1 mole) in absolute ethanol (50 ml) at (0-5 °C), when salt formation was completed, the white crystals formed, filtered and dried, m.p. 145-147 °C (lit. 145-146)⁽¹²⁾, 90% yield.

Ethyl glycinate (2)

Ammonia gas was passed through a solution of ethyl glycinate hydrochloride in methylene chloride with stirring. Ammonium chloride was filtered and the solvent was evaporated to give colorless oil, yield 81%, ν cm⁻¹ 1750 (C=O).

Ethyl arylidine glycinate (3,4)⁽¹³⁾

A mixture of ethyl glycinate (1 g, 0.01 mol), substituted benzaldehyde (0.01 mole) triethyl amine (0.91 g) in ethanol (50 ml) was refluxed for (3) hours, the mixture was filtered and the filtrate evaporated under reduced pressure, Tables (1,2).

Synthesis of hydrazides (5,6)⁽¹⁴⁾

A mixture of compounds (3 or 4) (0.08 mole), hydrazine hydrate (20 ml, 0.4 mole) in ethanol (50 ml) was refluxed for (3 h). Evaporation of the solvent under reduced pressure gave oily product, Table (1,2).

2-Arylidine methyl amino-1,3,4-oxadiazole-5-thiol (7,8)⁽¹⁵⁾

The hydrazide (5 or 6) (0.005 mole) was dissolved in ethanolic solution of sodium hydroxide (0.28 g, 0.005 mole/70 ml ethanol), carbon

disulfide (6 ml, 0.1 mole) was added slowly the mixture then refluxed for (16 h). the solvent was evaporated under reduced pressure and the residue was poured on crushed ice (30 g), the solution was acidified with dilute hydrochloric acid and left to stand for (20 h) for complete precipitation, the yellow solid was filtered, dried and recrystallized from ethanol, Tables (1,2).

5-Arylidine methyl amino-4-alkyl-1,2,4-triazole-3-thiol (9-16)⁽¹⁶⁾

A mixture of compound (7 or 8) (0.01 mole), and the amine (0.03 mole) in ethanol (25 ml) was refluxed for (4 h), the solvent then evaporated under reduced pressure, to give the corresponding triazoles, Tables (1,2).

1-Arylidine amino acetyl thiosemicarbazide (17,18)⁽¹⁷⁾

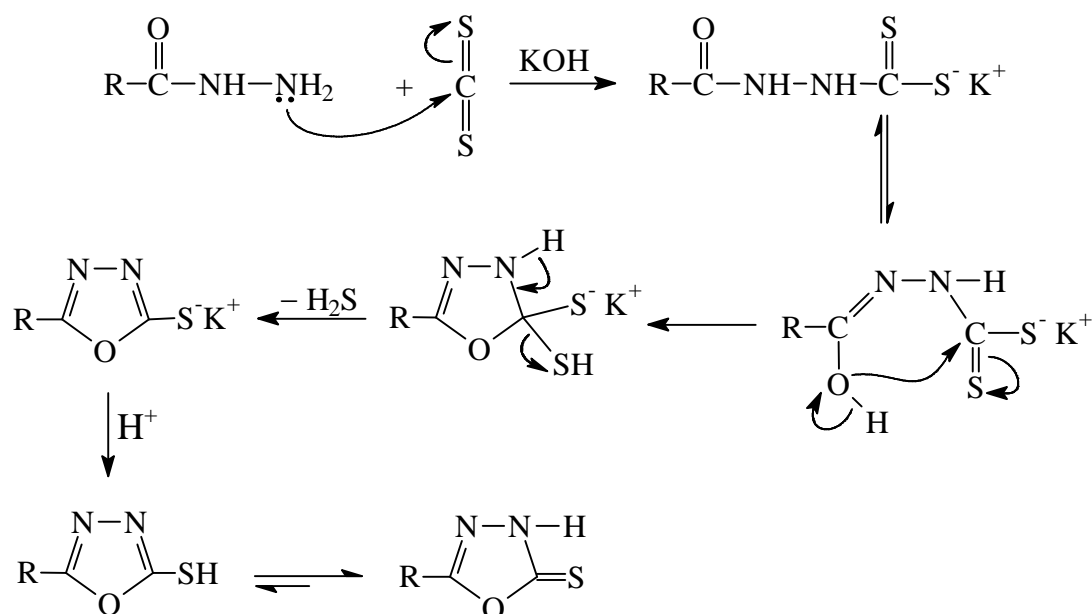
A mixture of hydrazide (5 or 6) (0.013 mole), ammonium thiocyanate (3 g, 0.039 mole) and hydrochloric acid (6 ml) in absolute ethanol (40 ml) was refluxed for (22 h), the solvent was removed under reduced pressure, the residue then added to crushed ice with stirring, the precipitate formed, filtered, dried and recrystallized from ethanol, Tables (1,2).

5-Arylidine methyl amino-1,2,4-triazole-3-thiol (19,20)

The substituted thiosemicarbazide (17 or 18) (0.005 mole) was dissolved in 1.5% sodium hydroxide solution (20 ml), the mixture was refluxed for (3 h), then the acidified with dilute hydrochloric acid with cooling to (pH 6), the formed solid was filtered, dried and recrystallized from ethanol-water, Tables (1,2).

RESULTS AND DISCUSSION:

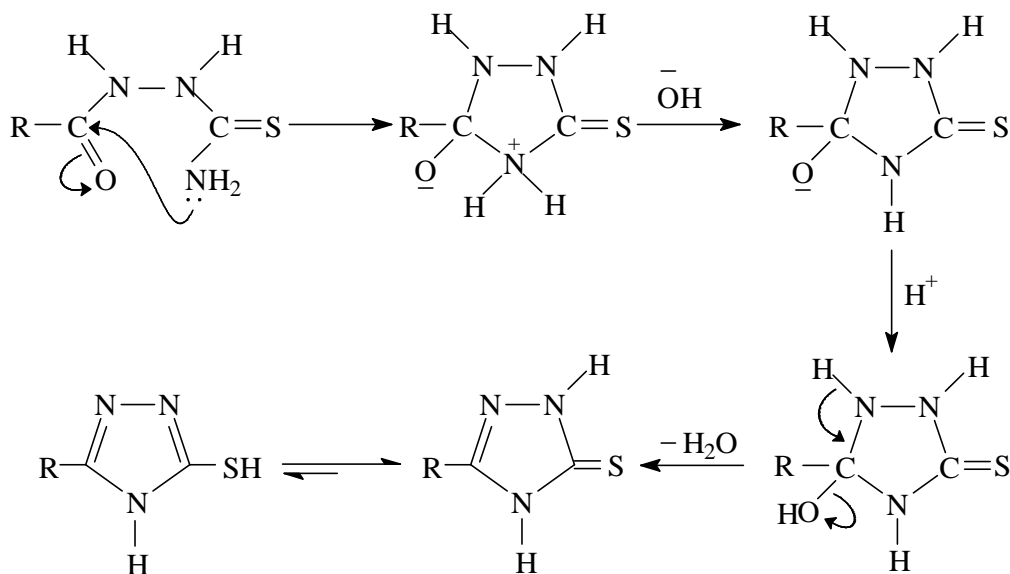
The synthesis of substituted 1,2,4-triazoles was achieved by a number of methods and starting from various compounds. In this work glycine was used as starting material, which converted to its ethyl ester via ethyl glycinate hydrochloride, the salt show absorption $\nu \text{ cm}^{-1}$ at 1750 (C=O). Ethyl glycinate was treated with substituted benzaldehyde to give ethyl aryldine glycinate (3,4), compound (3) show absorption $\nu \text{ cm}^{-1}$ at 1612 (C=N) and 1730 (C=O), λ_{max} 332 nm n- π^* transition. The esters then converted to acid hydrazides (5,6), hydrazide (5) show absorption $\nu \text{ cm}^{-1}$ at 3422 (N-H), 1682 (C=O) and 1624 (C=N), λ_{max} 360 nm n- π^* transition. The reaction of hydrazide (5 or 6) with carbon disulfide in ethanolic potassium hydroxide to give the corresponding 1,3,4-oxadiazoles (7,8), through the following mechanism⁽¹⁵⁾:



Oxadiazole (7) show absorption at $\nu \text{ cm}^{-1}$ 1641 (C=N), 1163 (C=S) acid 1050 (C-O-C), λ_{max} 336 nm n- π^* transition. The oxadiazole then converted to the substituted 1,2,4-triazoles (9-16).

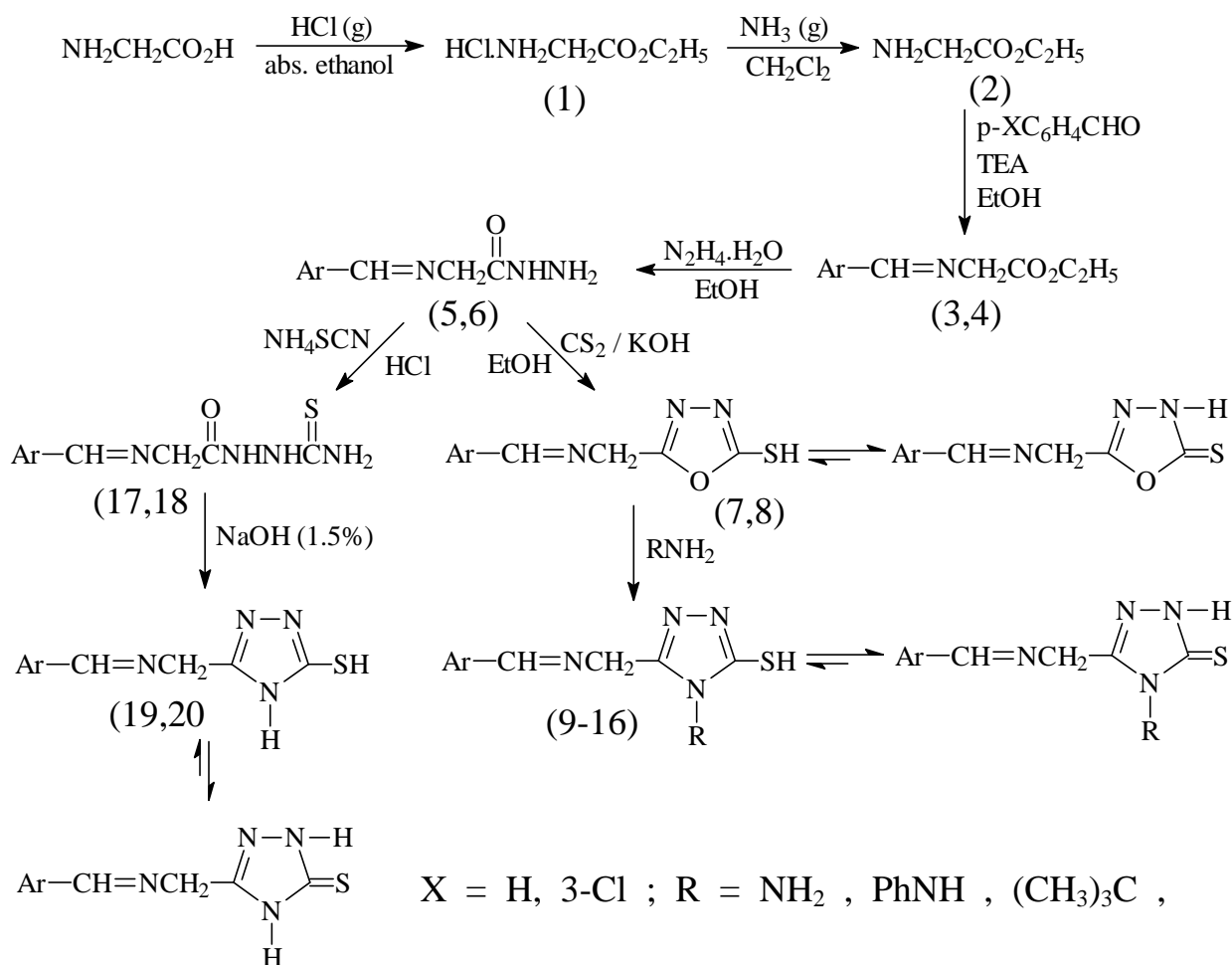
Triazole (9) show absorption at $\nu \text{ cm}^{-1}$ 1631 (C=N) and 1190 (C=S), λ_{max} 350 nm (n- π^* transition). Substituted thiosemicarbazides (17,18)

were synthesized from hydrazides (5,6) by their reaction with ammonium thiocyanate / hydrochloric acid, the thiosemicarbazide (17) show absorption at $\nu \text{ cm}^{-1}$ 1668 (C=O), 1632 (C=N) and 1210 (C=S), λ_{max} 330 nm (n- π^* transition). The thiosemicarbazides (17,18) were cyclized to substituted 1,2,4-triazoles (19,20) by sodium hydroxide, through the following mechanism⁽¹⁸⁾.



1,2,4-Triazole (19) showed absorption at $\nu \text{ cm}^{-1}$ 3358 (N-H), 1636 (C=N) and 1230 (C=S), λ_{max} 312 nm (n- π^* transition).

Physical and spectral data are listed in Tables (1,2).



Scheme (1)

Table (1): Physical data of compounds (3-20)

Comp. No.	Molecular formula	R	Ar	Yield %	m.p. (°C)
3	C ₁₁ H ₁₃ NO ₂	-	Ph	73	Oily
4	C ₁₁ H ₁₂ NO ₂ Cl	-	3-ClC ₆ H ₄	85	Oily
5	C ₉ H ₁₁ N ₃ O	-	Ph	80	Oily
6	C ₉ H ₁₀ N ₃ OCl	-	3-ClC ₆ H ₄	75	Oily
7	C ₁₀ H ₉ N ₃ O	-	Ph	90	145
8	C ₁₀ H ₈ N ₃ OCl	-	3-ClC ₆ H ₄	82	151
9	C ₁₀ H ₁₁ N ₅ S	NH ₂	Ph	60	183-185
10	C ₁₀ H ₁₀ N ₅ SCl	NH ₂	3-ClC ₆ H ₄	63	105-108
11	C ₁₆ H ₁₅ N ₅ S	PhNH	Ph	55	148-153
12	C ₁₆ H ₁₄ N ₅ SCl	PhNH	3-ClC ₆ H ₄	57	159-161
13	C ₁₄ H ₁₈ N ₅ S	(CH ₃) ₃ C	Ph	78	175-177
14	C ₁₄ H ₁₇ N ₅ SCl	(CH ₃) ₃ C	3-ClC ₆ H ₄	73	210-212
15	C ₁₆ H ₂₂ N ₅ S	CH ₃ (CH ₂) ₅	Ph	70	130-132
16	C ₁₆ H ₂₁ N ₅ SCl	CH ₃ (CH ₂) ₅	3-ClC ₆ H ₄	72	95-97
17	C ₁₀ H ₁₂ N ₄ OS	-	Ph	60	199-201
18	C ₁₀ H ₁₀ N ₄ S	-	3-ClC ₆ H ₄	66	214-217
19	C ₁₀ H ₁₁ N ₄ OSCl	-	Ph	42	71-73
20	C ₁₀ H ₉ N ₄ SCl	-	3-ClC ₆ H ₄	30	158-161

Table (2): Spectral data of compounds (3-20)

Comp. No.	IR ν cm ⁻¹ , KBr					U.V. EtOH, λ_{\max}
	C=O	N-H	C=N	C-O-C	C=S	
3	1730		1612			332
4	1738		1610			325
5	1682	3422	1624			360
6	1670	3395	1636			356
7			1641	1050	1163	336
8			1643	1014	1182	348
9			1631		1190	350
10			1639		1207	314
11			1646		1183	343
12			1635		1217	318
13			1624		1210	320
14			1641		1186	312
15			1654		1175	304
16			1637		1194	306
17	1668		1632		1210	330
18	1670		1650		1198	360
19		3358	1636		1230	312
20		3422	1652		1225	340

REFERENCES

1. F.X. Mathy, B. Broman, D. Ntivunwa, A.J.D. Winne, R. Verbeeck and V. Preat, (2003), "On-line determination of fluconazol in blood and dernal rat microdialysates by microbore high performance liquid chromatography", *J. of Chromatography B. Vol.*, 787, 323.
2. S.S. Malsomoto; J.M. Fujitaki; L.D. Nord and R.C. Willis, (1990), "Inhibition of pyrimidine metabolism in myeloid leukemia cells by triazole and pyrazol nuleosides", *Biochem. Pharmacol.*, 39, 455; *Chem. Abstr.*, (1990), Vol. 112, p.171869a.
3. S.C. Benner, V.B. Jigajiani and V.V. Badiyer, (1976), "Pyrimidines VI, Synthesis of 2-methyl thio-5-bromo pyrimidine-4-carboxylic acid thiosemicarbazides, 3-pyrimidy-1,2,4(H)-triazole and 2-aryl amino-1,3,4-thiadiazoles", *Rev. Roum. Chim.*, 21, 5, 757; *Chem. Abst.*, (1976), 85, 94306j.
4. S.C. Benner, V.B. Jigajiani and V.V. Badiyer, (1976), "Pyrimidines VI, Synthesis of 2-methyl thio-5-bromo pyrimidine-4-carboxylic acid thiosemicarbazides, 3-pyrimidy-1,2,4(H)-triazole and 2-aryl amino-1,3,4-thiadiazole", *Rev. Roum. Chim.*, 21, 5, 757; *Chem. Abst.*, (1976), 85, 94306j.
5. P.J. Kothari, S.P. Singh, S.S. Parmar and V.I. Stenberg, (1980), "Synthesis of some newer 5-(5-aryl-2H-tetrazole-2-yl-methyl)-4-substituted-5-triazole-3-thiols as possible anti-inflammatory agent", *J. Heterocyclic Chem.*, 17, 1393.
6. C. Bing; Q. Xuhong; C. Song; L. Haidong and S. Gonghua, (2003), "Synthesis and insecticidal activity of 1,2,4-triazole derivatives", *Arkivoc*, (ii), p.141.
7. L.Z. Xu, K. Jiao, S.S. Zhang and S.P. Kuang, (2002), "Studies on synthesis and biological activity of novel triazol compound containing

- N,N-dialkyldithiocarbamate”, *Bull. Korean Chem. Soc.*, Vol. 23, No. 12, p. 1699.
8. P.J. Kothari, V. Kishore, V.I. Stenberg and S.S. Parmer, (1978), “Synthesis of 5-(1-naphthylmethyl)-4-aryl-S-triazole-3-thiol/yl-thioglycolic acids as possible anti-inflammatory agents”, *J. Heterocyclic Chem.*, 15, 1101.
 9. A. Shafiee, E. Naimi, P. Mansobi, F.P. Foroumadi and M. Serkari, (1995), “Synthesis of substituted-oxazolo-1,3,4-thiadiazoles, 1,3,4-oxadiazoles and 1,2,4-triazoles”, *J. Heterocyclic Chem.*, 32, 1235.
 10. E.B. Vasileve, D.V. Sevenard, O.G. Knomutov, O.A. Kuznetsova, N.S. Karpenko and V.I. Filyakova, (2003), “Synthesis of trifluoroalkyl- and fluoroaryl-substituted 4,5-dihydro-1H-1,2,4-triazole-5-thione”, *Russian Academy of Science; Chem. Abst.*, P. 874. (Internet)
 11. J.P. Milhim, (1997), “Synthesis and reaction of novel fluorine containing indolo-triazine compounds”, *Babylon Univ. Journal*, 2, 3, 367.
 12. M.N. Ibrahim, M.S. Saeed and S. Fadi, (1987), “Synthesis studies of dihydro peptides. Part II”, *J. Iraq. Chem. Soc.*, 12, 159.
 13. H. El-Masry, H.H. Fahmy and S.H.A. Abdelwahed, (2000), “Synthesis and antimicrobial activity of some new benzimidazole derivatives”, *Molecules*, 5, 1429-1438.
 14. H.L. Yale, K. Losee, J. Martins, M. Holsing, F.M. Perry and J. Bernstein, (1953), “Chemotherapy of experimental tuberculosis. VIII. The synthesis of acid hydrazides, Their derivatives and related compounds”, *J. Am. Chem. Soc.*, 75, p. 1933.
 15. R. W. Young and K. H. Wood, (1955), “The cyclization of 3-acyl dithiocarbazates esters”, *J. Am. Chem. Soc.*, Vol. 77, p. 400.

- 16.Y.A. Al-Soud and N.A. AL-Masoudi, (2003), "Anew class of dihaloquinolones bearing N-aldehydoglycosylhydrazides, mercapto-1,2,4-triazole, oxadiazoline and α -Aminoester precursors: synthesis and antimicrobial activity", J. Braz. Chem. Soc., Vol. 14, No. 15, pp. 790-796.
- 17.M.T. Wu, (1972), "Synthesis of some heterocyclic derivatives of 3,5-dinitro o-toluic acid", J. Heterocyclic Chem., 9, 31.
- 18.K.H. Al-Naimi, (2000), "Synthesis and study of some biologically active five membered ring heterocyclic compounds derived from substituted cinchophen", Ph.D. Thesis, Mosul University.