Synthesis of some substituted 1,3,4-oxadiazoles, thiadiazoles and 1,2,4-triazoles

Shereen R. Mohamed
Chemistry Department / College of Education
Dohuk University

Received 31 / 03 / 2008 **Accepted** 22 / 07 / 2008

الخلاصة

تم في هذا البحث تحضير عدد من معو ضات ٤،٣،١-اوكسادايازول و ٤،٣،١-ثايادايازول و ٤،٢،١-ترايازول. حول ميثاكريلات الاثيل إلى الهيدرازيد المقابل (١) من خلال تفاعله مع الهيدرازين المائي في الايثانول . تم تحويل الهيدرازيد الى ثايوسيميكاربازيد المعوض (٢). أعطى تفاعل الثايوسيميكاربازيد المعوض مع محل ول هيدروكسيد الصوديوم ومع حامض الكبريتيك المركز ٥-معوض- ٤،٢،١-ترايازول- ٣-ثايول (٣) و ٢-معوض- ٥-امينو- ٤،٣،١-ثايادايازول (٤) على التوالي. تم مفاعلة هيدرازيد الحامض (١) مع البنزالديهايد أو احد معوضاته ليعطي الهيدرازونات المقابلة (٧-١٢) والتي تم حولقتها باستخدام ثنائي اوكسيد الرصاص إلى ٢-معوض- ٥-فنيل- ٤،٣،١-اوكسادايازول (١٤). أعطى تفاعل هيدرازيد الحامض مع حامض الفورميك ١-فورميل ٢-اسيل هيدرازين (٦) والذي تم تحويله الى ٤،٣،١-اوكسادايازول أحادي التعويض (١٣) من خلال تفاعله م ع خماسي اوكسيد الفسفور. تم مفاعلة هيدرازيد الحامض (١) مع ايسوثايوسيانات الفنيل ليعطي ثايوسيميكاربازيد معوض (٥). شخصت المركبات المحضرة بالطرق الفيزياوية والطيفية.

ABSTRACT

In this paper the synthesis of some substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles is reported. Ethyl methacrylate was treated with hydrazine hydrate in ethanol to give the corresponding hydrazide (1). The hydrazide was converted to 1-acyl thiosemicarbazide (2) byits reaction with ammonium thiocyanate, which was treated with sodium hydroxide solution and with concentrated sulfuric acid to give 5-substituted-1,2,4-triazoles-3-thiol (3) and 2-substituted-5-amino-1,3,4-

thiadiazole (4) respectively. The acid hydrazide (1) was treated with benzaldehyde or substituted benzaldehyde to give hydrazones (7-12), the hydrazones were then cyclized with lead dioxide to 2-subtituted-5-phenyl 1,3,4-oxadiazole (14). The reaction of the hydrazide (1) with formic acid gave 1-formyl-2-acyl hydrazine (6) and the cyclization of (6) by phosphorus pentaoxide gave monosubstituted-1,3,4-oxadiazoles (13). Acid hydrazide (1) was treated with phenyl isothiocyanate to give substituted thiosemicarbazide (5).

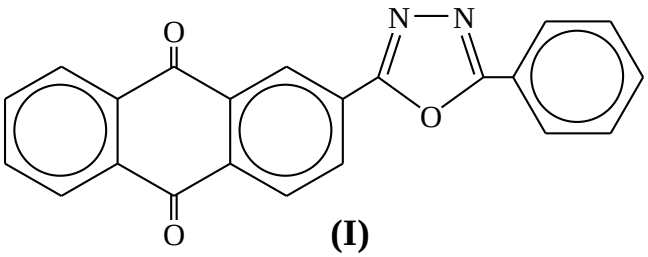
The structure of the synthesized compounds were confirmed by physical and spectral means.

INTRODUCTION

1,3,4-oxidiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles and their derivatives are associated with various biological activities such as anticonvulsant[1], antifungal[2,3], anticancer[4,5], anti-inflammatory[6,7] and antibacterial properties[8-10]. The therapeutic effect of these compounds have been well studies for a number of pathological cases including inflammation[11], pain[12] or hypertension[13].

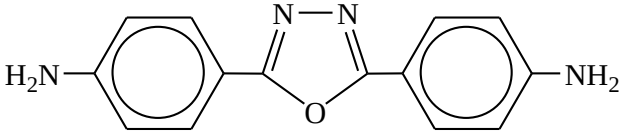
These biological data promoted many researchers to synthesized substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole by using a number of starting materials and methods. 1,3,4-Oxadiazoles were synthesized from acid hydrazides by their reaction with carbon disulfide in ethanolic potassium hydroxide[14,15].

1,2-Diacyl hydrazine was treated with thionyl chloride to give substituted 1,3,4-oxdiazole, such as compound (I)[16].



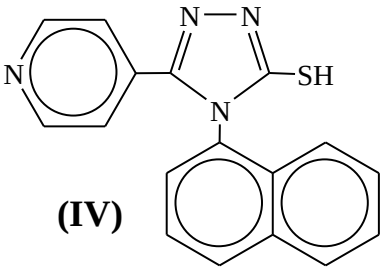
(I)

Whereas oxidation of substituted thiosemicarbazide with lead oxide[17] or potassium iodide/iodine[18] gave substituted 1,3,4-oxadiazoles. Treatment of carboxylic acids with hydrazine in the presence of polyphosphoric acid gave 1,3,4-oxdiazolee as compound (II).

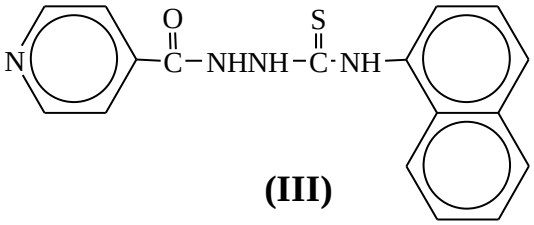


(II)

Substituted 1,3,4-thiadiazoles were synthesized from substituted thiosemicarbazides by their reaction with concentrated sulfuric acid[19] or methyl sulfonate[20]. Substituted 1,2,4-triazoles were synthesized from substituted thiosemicarbazide by its treatment with sodium hydroxide solution as the cconversion of (III) to (IV)[21].



(IV)



(III)

4-Amino-3,5-diphenyl-1,2,4-trizole was prepared by heating benzoic acid hydrazide to (200º C)[22].

In the present study some new 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,3,4-triazoles have been synthesized .

EXPERIMENTAL

The chemicals were purchased from Fluka 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., using KBr discs. UV spectra were recorded on Shimadzu, UV-160, UV-Visible Recording Spectrophotometer.

Methacrylic acid hydrazide (1)

A mixture of ethyl methacrylate (5.68 g, 0.04 mole) and hydrazine hydrate (0.2 mole) in absolute ethanol (30 ml) was refluxed for 3 hours. The solvent was evaporated to give the hydrazide as a white powder, (Tables 1,2).

1- Acyl thiosemicarbazide (2)

A mixture of acid hydrazide (1) (1.44 g, 0.02 mole), ammonium thiocyanate (4.56 g, 0.06 mole), concentrated hydrochloric acid (8 ml) in absolute ethanol (50 ml) was refluxed for 22 hrs. The solvent was evaporated and residue poured on crushed ice with stirring. The solid materials which; formed was filtered off, dried and recrystallized from ethanol (Tables 1,2).

5-(Propene-2-yl)-1,2,4-triazole-3-thiol (3)

A mixture of substituted thiosemicarbazide (2) (1.59 g, 0.01 mole) and 2% aqueous sodium hydroxide solution (15 ml) was refluxed for 3

hrs. The mixture was treated with charcoal and the charcoal then removed by hot filtration, the filtrate was acidified by 10% hydrochloric acid with cooling. The precipitate was filtered and recrystallized from ethanol (Tables 1,2).

2-(Propene-2-yl)-5-amino-1,3,4-thiadiazole (4)

Concentrated sulfuric acid (10 ml) was added to substituted thiosemicarbazide (2) (0.79 g, 0.05 mole). The mixture was heated on water bath 90 º C with stirring for 2hrs., the mixture then poured onto ice-water and neutralized with concentrated ammonia solution with cooling, the formed precipitate was filtered washed with cold water, dried and recrystallized from benzene (Tale 1,2).

1-(2-Methyl propenoyl)-4-phenyl thiosemicarbazide (5)

A mixture of acid hydrazide (1) (1.44 g, 0.02 mole), phenyl isothiocyanate (8.1 g, 0.06 mole) and concentrated hydrochloric acid (8 mole) in ethanol (50 ml) was refluxed for (10) hrs., the solvent was evaporated and the residue poured on crushed ice, the solid then filtered off, dried and recrystallized from ethanol (Tables 1,2).

1-(2-methyl propenoyl)-2-formyl hydrazine (6)

A mixture of acid hydrazide (1) (0.72 g, 0.01 mole) formic acid (0.92 g, 0.02 mole) in ethanol (20 ml) was refluxed for 3 hrs., the mixture was cooled and the solid filtered off dried and recrystallized from ethanol (Tables 1,2).

Hydrazones (7-12)

A mixture of benzaldehyde / substituted benzaldehyde (0.01 mole) and acid hydrazide (1) (0.72 g, 0.01 mole) in ethanol (20 mole) was refluxed for (2) hrs. The mixture was condensed and the precipitate was filtered and recrystallized from benzene (Tables 1,2).

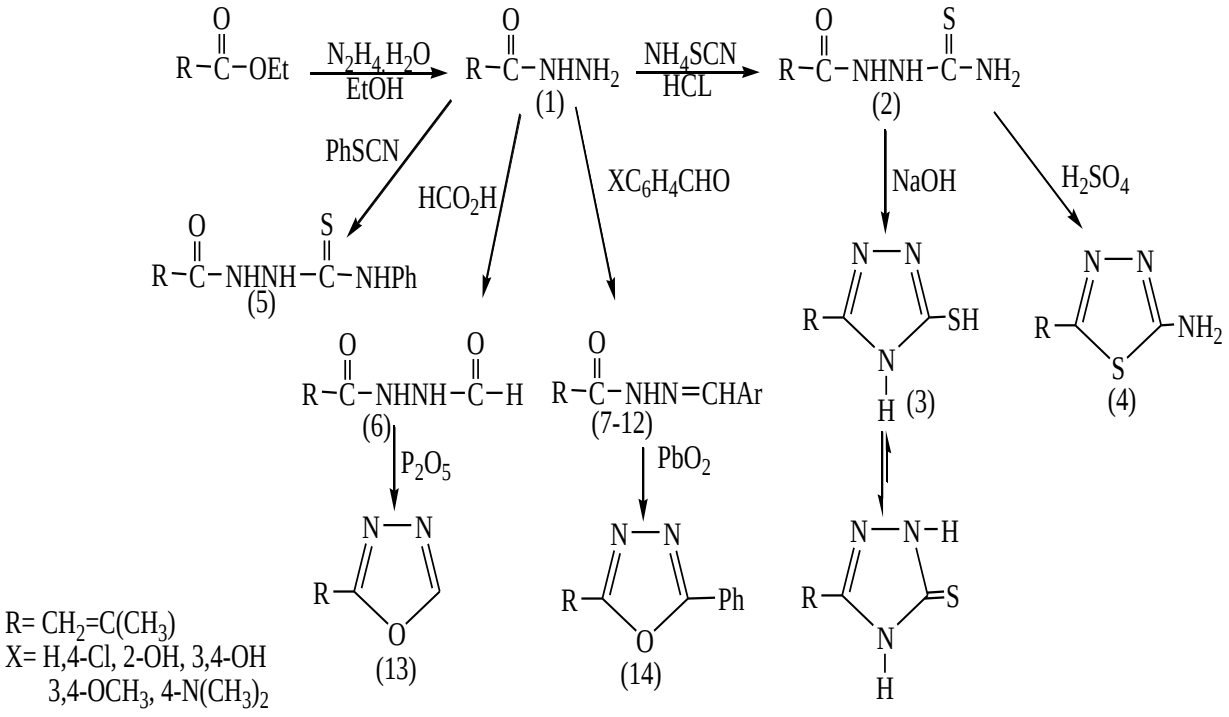
Cyclization of 1-(2-methyl propenoyl)-2-formyl hydrazine (6) to 2-(propene-2-yl)-1,3,4-oxadiazole (13)

Phosphorous pentaoxide (1.42 g, 0.01 mole) was added to a solution of 1-formyl-2-acyl hydrazine (6) (0.01 mole) in dry xylene (40 ml). The mixture was refluxed for 3 hrs., the solvent was evaporated and the residue washed with water, dried and crystallized from ethanol (Tables 1,2).

Cyclization of the hydrazone (7) to substituted 1,3,4-oxadiazole (14)

To a homogenous solution of hydrazones (7) (0.01 mole) in 20 ml of glacial acetic acid, PbO_2 (2.39 g, 0.01 mole) was added, the mixture

then stirred with mechanical stirrer at 25 º C for 1 hr. The reaction mixture was diluted with ice-water and left to stand for 24 hrs. The precipitate was filtered off and recrystallized from benzene (Tables 1,2).

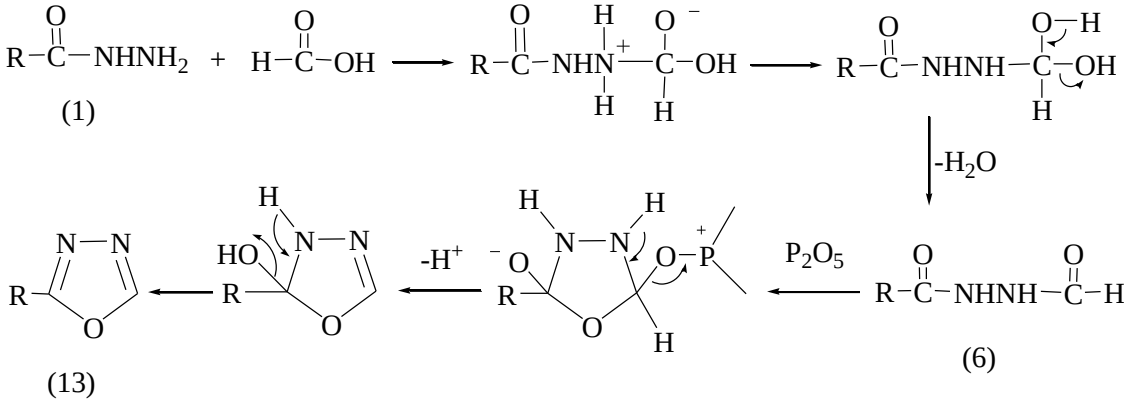


Scheme (1)

RESULTS AND DISUSSION

In the paper the synthesis of mono and disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles from ethyl methacrylate is reported (Scheme 1). Ethyl methacrylate was treated with hydrazine hydrate in ethanol to give the acid hydrazide (1). Acid hydrazide (1) was treated with phenyl isothiocyanate to give substituted thiosemicarbazide (5), while treatment of acid hydrazide (1) with ammonium thiocyanate gave substituted thiosemicarbazide (2), treatment of thiosemicarbazide (2) with sodium hydroxide solution and with concentrated sulfuric aid gave 5-substituted-1,2,4-triazole-3-thiol (3) and 2-substituted-5-amino-1,3,4-thiadiazole (4) respectively.

The IR spectrum of compound (1) showed the following peaks (v cm^{-1}) 3311 (N-H), 1654 (C=O), 1605 (C=C); compound (2) 3355 (N-H), 1676 (C=O), 1608 (C=C), 1285 (C=S), compound (3) 3380 (N-H), 1636 (C=N), 1609 (C=C), 1150 (C=S); compound (4), 3276 (N-H), 1637 (C=N), 1615 (C=C) and 1039 (-S-C), compound (5) 3211 (N-H), 1660 (C=O), 1610 (C=C), 1189 (C=S). hydrazide (1) was treated with formic acid to give 1-(2-methyl propenoyl)-2-formyl hydrazine (6), compound (6) was cyclized by phosphorous pentaoxide to give 2-substituted-1,3,4-oxadiazole (13) according to the following suggested mechanism:

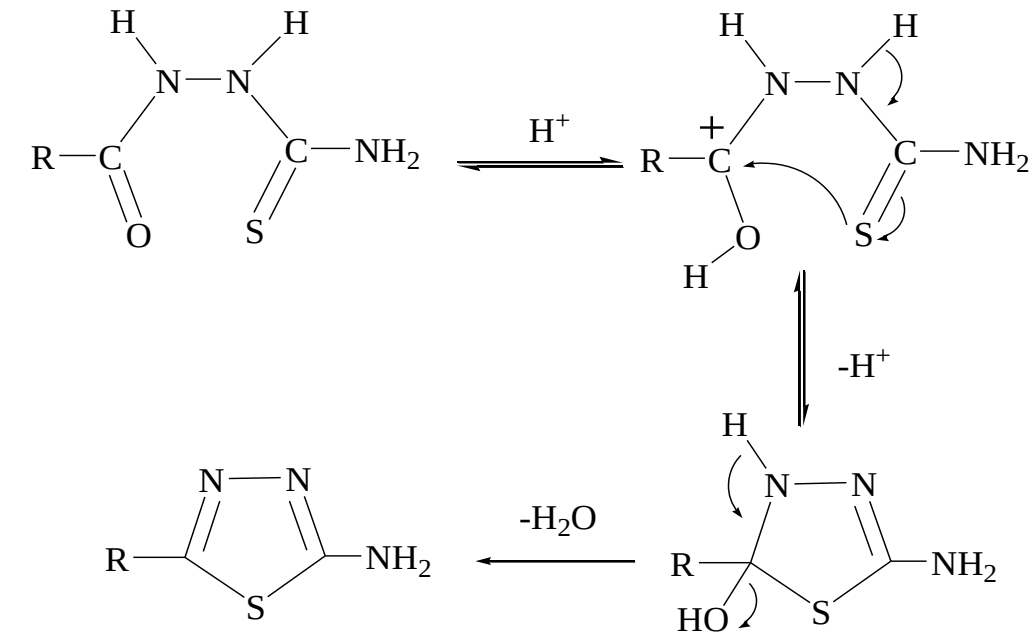


Treatment of compound (1) with benzaldehyde or substituted benzaldehyde gave hydrazones (7-12). The hydrazone (7) was treated with lead dioxide to give 2-(propene-2-yl)-5-phenyl-1,3,4-oxadiazole (14).

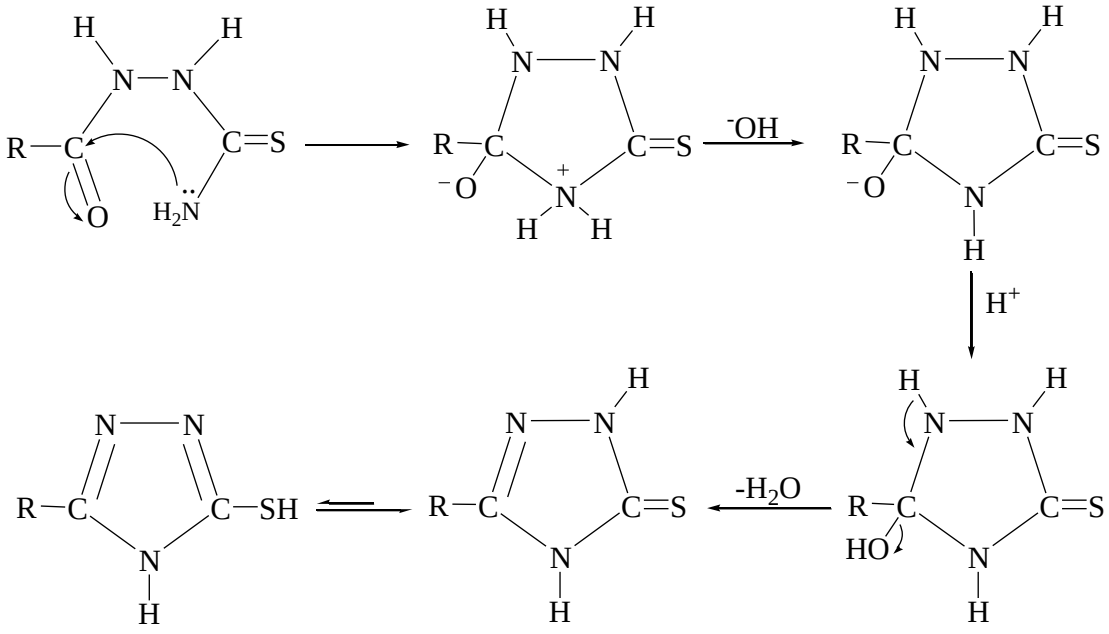
IR, v (cm^{-1}) for compound (6), 3445 (N-H),1675 (C=O), 1625 (C=C); compound (7-12) 3422-3207 (N-H), 1688-1650 (C=O), 1624-1601(C=C), 1651-1632 (C=N), compound (13), 1649 (C=N), 1071 (C-O-C); compound (14) 1628 (C=N), 1600 (C=C), 1072 (C-O-C).

The ultraviolet spectra of the synthesised compound were recorded using chloroform as solvent and the λ_{max} data shown in Table (2).

The formation of substituted 1,3,4-thiadiazole and substituted 1,2,4-triazole may proceed through the mechanisms 1 and 2 respectively.



Mechanism (1)



Mechanism (2)

Table (1): Physical constants of compounds (1-14)

Comp. No.	X	%yield	m.p. (º C)	Color
1	.	85	210-212	White
2	.	72	203-205	White
3	.	65	230-231	Gray
4	.	76	215-217	White
5	.	60	182-183	Green
6	.	44	149-151	White
7	H	57	122-123	Yellow
8	4-Cl	55	214-216	Yellow
9	2-OH	61	210-211	Pale yellow
10	3,4-OH	45	150-153	Brown
11	3,4-OCH_3	77	172-174	Pale yellow
12	4-NMe_2	53	166-167	Deep yellow
13	.	49	190-192	Pale green
14	.	56	>300	Pale brown

Table (2): Spectral data of compounds (1-14)

Comp. No.	IR (KBr) v cm^{-1}					UV , $CHCl_3$ λ_{max} (nm)
	C=O	N-H	C=C	C=N	Others	
1	1654	3311	1605	.	.	252
2	1676	3355	1608	.	1285(C=S)	280
3	.	3380	1609	1636	1150 (C=S)	261
4	.	3276	1615	1637	1039 (C-S-C)	294
5	1660	3211	1610	.	1189 (C=S)	255
6	1675	3445	1625	.	.	247
7	1660	3303	1624	1654	.	297
8	1654	3413	1620	1632	.	293
9	1688	3422	1619	1638	.	294
10	1662	3387	1610	1642	.	246
11	1600	3207	1602	1651	.	293
12	1668	3420	1601	1646	.	281
13	.	.	١٦٠٨	1649	1071 (C-O-C)	244
14	.	.	1600	1628	1072 (C-O-C)	251

REFERENECS

1. Kane J. M., Baron B. M., Dudley M. W., Sorensen S. M., Staeger M. A. and Miller F. P., J. Med. Chem., 33, 2772, (1990).

2. Rollas S., Kalyoncuoglu N., Sur-Altiner D. and Yegenoglu Y., Pharmazie, 48, 308, (1993).

3. Chollet J. F., Bonnemain J. L., Migiuniac L. and Rohr O. J., Pestic. Sci., 29, 427, (1990).

4. Holla B. S., Veerendra B., Shivanande M. K. and Poojary B., European Med. Chem., 38. 759, (2003).

5. Bekircan O., Kucuk M., Kahveci B. and Kolayli S., Arch. Pharm., 338, 365, (2005).

6. Wade P. C., Vogt B. R., Kissick T. P., Simpkins L. M., Palmer D. M. and Millomig R. C., J. Med. Chem., 25, 331, (1982).

7. Modzelewska B. and Kalabeeen, J. Pharmazie, 54, 503, (1999).

8. Malbec F., Milcent R., Vicart P. and Bure A. M., J. Heterocyclic Chem.., 21, 1769, (1984).

9. Milcent R., Vicart P. and Bure A. M., Eur. J. Med. Chim., 18, 215, (1983).

10. Gulerman N., Rollas S., Kiraz M., Ekinci A. C. and Vidin A., II Farmaco., 52, 691, (1997).

11. Palaska E., Sahim G., Kelicen P., Durlu N. T. and Altinok G., Farmaco., 57, 101, (2002).

12. Onkol T., Cokir B. and Sahin M. F., Turk. J. Chem., 28, 461, (2004).

13. Baldwin J. J., Engelhardt E. L., Hirschmann R., Ponticello G. S., Atkinson J. G., Wasson B., Sweet C. S. and Scriabine A., J. Med. Chem., 23, 65, (1980).

14. Amir M. and Shahani S., Indian j. Heterocccycli Chem., 8(2), 107, (1998).

15. El-Masry A. H., Fahmy H. H. and Abdulwahed S. H. A., Molecules, 5, 1429, (2000).

16. Klingsberg E., J. Am. Chem. Soc., 5788, (1958).

17. Yousif K. H., Ph. D. Thesis, University of Mosul, (2000).

18. Hogal M. B. and Deshmukh D. J., Indian Chem. Soc., 66, 212, (1989).

19. Wu M. T., J. Heterocyclic Chem., 9, 31, (1972).

20. Kress T. J. and Costantino S. M., J. Heterocyclic Chem., 17, 607, (1980).

21. Zamani K., Faghihi K., Tofighi T. and Shariatzadeh M. R., Turk. J. Chem., 28, 91, (2004).

22. Shafiee A., Naimi E., Mansobi O., Foroumadi F. P. and Serkari M., J. Heterocyclic Chem., 32, 1235, (1995).