------ Raf. Jou. Sci., Vol. 22, No.3 pp 62- 75, 2011------

The Use of 3-Benzylidene Phthalide as Precursor to Synthesize New 1,3,4-Oxadiazole Derivatives

Shaymaa K. Younis
Department of Chemistry
College of Science
University of Mosul

Email : khazaalyounis @ yahoo . com

(Received 1/ 11 / 2010 ; Accepted 25 / 4 / 2011)

ABSTRACT

A series of new 2,5-disubstituted 1,3,4-oxadiazoles represented by compounds 2-phenyl-1-(2-(5-(5-aryl-1,3,4-oxadiazol-2-yl amino)-4H-1,2,4-triazol-3-yl)phenyl)ethanone (5a-f) have been synthesized from(Z)-3-benzylidene phthalide as useful precursor. 3-Benzylidene phthalide was reacted, firstly with urea under microwave irradiation and dry conditions to afford the corresponding 1-(2-(α-phenylacetyl)benzoyl)urea (1). The later compound underwent cycloaddition reaction with hydrazine hydrate (80%) to give 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone (2), which upon reaction with ethyl chloroformate provided the corresponding ethyl- 5-(2-(α-phenylacetyl)phenyl)-4H-1,2,4-triazol-3-yl carbamate (3).

4-(5-(2-(α-Phenylacetyl)phenyl)-4H-1,2,4-triazol-3-yl) semicarbazide (4) was also prepared from the reaction of compound (3) with hydrazine hydrate (80%) under mild conditions. Finally, 2-phenyl-1-(2-(5-(5-aryl-1,3,4-oxadiazol-2-yl amino)-4H-1,2,4-triazole-3-yl)phenyl) ethanone (5a-f) were obtained via the reaction of compound (4) with various substituted benzoic acid by the action of phosphorous oxychloride. The structure of the prepared compounds were confirmed by the available physical and spectral methods.

Key words: (Z)-3-benzylidene phthalide; 1,3,4-oxadiazole derivatives; 1,2,4-triazole; Semicarbazide.

استخدام 3- بنزاليليدين فثاليد كمادة اولية مناسبة لتحضير عدد من مركبات 4,3,1-اوكساديازول الجديدة

الملخص

حضرت سلسة جديدة من مركبات 4,3,1-اوكساديازول-5,2-ثنائي التعويض والمتمثلة بالمركبات 2-فنيل-1-(2-(5-(5-اريل-1،3،4-اوكساديازول-2-يل امينو)-4هيدرو-1،2،4-ترايازول-3-يل)فنيل)ايثانون (5a-f) ابتداً من (سس)- 3-بنزاليليدين فثاليد بصفة مادة أولية مناسبة.

يتفاعل 3- بنزاليليدين فثاليد مع اليوريا باستخدام التشعيع بالموجات الدقيقة وفي ظروف جافة ليعطي المركب 1-(2-(α-اسيتيل فنيل) بنزويل) يوريا (1) المقابل. ادخل المركب الأخير في تفاعل إضافة حلقية مع الهيدرازين المائي (80%) وقد أعطى المركب1-(2-(5-امينو-4هيدرو-1،2،4-ترايازول-3-يل) فنيل)-2-فنيل ايثانون (2) والذي عند مفاعلته مع كلورو فورمات الاثيل أعطى المركب 5-(2-(α-اسيتيل فنيل) فنيل)-4هيدرو-1،2،4-ترايازول-3-يل كارباميت(3) المقابل.

أما المركب 4-(5-(2-(α-اسيتيل فنيل) فنيل)-4هيدرو-1،2،4-ترايازول-3-يل) سيميكاربازيد (4) فقد حضر من تفاعل المركب (3) مع الهيدرازين المائي (80%) في ظروف معتدلة.

وأخيرا فقد تم تحضير المركبات 5-فنيل-1-(2-(5-(5-اريل-4,3,1-اوكساديازول-2-يل امينو)-4هيدرو-4,2,1- ترايازول -3-يل) فنيل) ايثانون (5a-f) من خلال تفاعل المركب (4) مع عدد من معوضات حامض البنزويك بوجود ثلاثي كلورو اوكسيد الفسفور. شخصت جميع المركبات المحضرة باستخدام الطرائق الفيزياوية والطيفية المتوفرة.

INTRODUCTION

Heterocyclic compounds have a great deal of attention because of their biological activity and also they make possible development of novel material with unique properties (Mostafa, 2010; Arulmurugan and Kavitha, 2010; Srinivas and Kumar, 2010; Caiazzo *et al*, 2004). One very interesting and promising class of heterocyclic is the series of 2,5-disubstituted-1,3,4-oxadiazoles that have been proven to be effective antimicrobial, anti-inflammatory, fungicidal and bactericidal agents (Sharma *et al*., 2010; Narasimhan *et al*.,2010; Banday *et al*., 2010; Dewangan *et al*., 2010; Bari *et al*., 2008). Furthermore, the 1,3,4-oxadiazole nucleus is associated with divers pharmaceutical activities as antitumor, antitubercular, antimalariea and analagesic (Revanasiddappa and Subrahmanyam, 2010; Patel and Patel, 2010; Mitsui and Aoki, 2010; Husain and Ajmal, 2009; He *et al*., 2009). On the other hand, these compounds have

been extensively employed in industrial and agrecultural field (Naik *et al*., 2009; Jain *et al*., 2009; Kim and Kang, 2008; Awadallah, 2006).

In this presentation, (Z)-3-benzylidene phthalide which is another type of heterocyclic was used as useful precursor to obtaind 1,3,4-oxadiazoles. Optionally, 3-substituted phthalides have wide applications in idusterial field (Shibata and Gaesser, 1991; Scholl *et al*., 1989; Conner, 1982) and also have emerged as inexpensive and easily available reagents in organic synthesis (Dalloul, 2010; Viña *et al*., 2009; del Olmo *et al*., 2006; Rios and Delgado, 1999; Hrnčiar et al., 1994; Humber, 1974; Rosenthal and Yalpani, 1965; Litvan and Stoll, 1958). Moreover, these compounds are known to possess multiple biological activities (Kurume *et al*., 2008; Kanazawa and Terada, 2007; Kundu *et al*., 1998; Ganji *et al*., 1993; Ibrahim, 1991). Several 3-substituted phthalides have been isolated from natural source and also used extensively as intermediat for the synthesis of varous drugs and naturally occuring compounds (Tang *et al*., 2010; Phan *et al*., 2009; Patil and Karnik, 2007).

In this resaerch, it is planned to generate a new series of 2,5-disubstituted-1,3,4-oxadiazoles represented by compounds (5a-f), (Z)-3-benzylidene phthalide firstly was reacted with urea to prepar compound (1) and the latter will be used as key intermediat to synthesize 1,2,4-triazole represented by compound (2) which was in turn used as useful material to prepar 1,3,4-oxadiazoles compounds (5a-f).

EXPERIMENTAL

Melting points (M.P.) were measured on Electrothermal, Gallenkamp melting point apparatus and are uncorrected. Proton-Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded using, spectrophotometer (H300MHz); with TMS as internal standard, and DMSO-d_6 as solvents; Jorden, University of Al-Bayt. [(s) singlet; (t) triplet; (q) quarlet; (m) multiplet].Infrared (FT-IR) spectra were recorded as (KBr) disc using FT-IR-600, Biotech Engineering Mangement CO. LTD. (UK). Ultraviolet (UV) spectra were performed on Shimadzu UV-Visible spectrophotometer UV-1650 PC using methanol as a solvent. The microwave oven is a domestic microwave oven (LG, MS-192W), (360watt) was used. The starting material (Z)-3-benzylidene phthalide was manufactured via Fluka Com. (Germany). Finally, thin layer chromatography (TLC) were carried out on silica gel (120 mesh) coated plates (2x10) cm, activated for one hour at (110-120°C) before use.

Synthesis of 1-(2-(α-phenylacetyl)benzoyl)urea (1): (Ilango *et al*, 2010; Benjamin and Hijji, 2007)

A mixture of (Z)-3- benzylidene phthalide (0.01 mole, 2.22 gm) and urea (0.01mole, 0.6 gm) was irradiated in microwave oven for (4 min.) at (360 watt). The reaction mixture was cooled down to room temperature, water was added and the mixture was washed thoroughly with water. The crude product was purified by recrystallization from methanol to yield compound (1) (1.9 gm), m.p. (79-80°C) in (72%) yield. The purity of the obtained product was controlled by TLC technique using solvent system (ethyl acetate: acetone) in (9:1) ratio, R_f value (0.451), H^1-NMR (DMSO-d6) δ /ppm: 3.5 (s,2H,CH_2), 6.7 (s,2H,NH_2), 7.1-8.2 (m,H-

aromatic) and 10.7 (s,1H,NH), FT-IR (KBr) υ /cm^{-1}: 3205 (NH_2), 1677 (C=O ketone) and 1657 (C=O amide), UV (methanol) λ_{max} : 226 nm.

Synthesis of 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone (2): (Şener, 2004)

Excess of hydrazine hydrate (80%) (0.08 mole, 4 ml) was added to compound (1) (0.007 mole, 1.96 gm) in ethanol (30 ml) with a catalytic amount of triethyl amine (1ml). The reaction mixture was heated under reflux for (4 hrs.) with stirring and was then left to cool at room temperature. The precipitate that formed was filtered off, dried and recrstallized from ethanol to give compound (2) (1.85 gm), m.p. (192-193°C) in (96%) yield. The purity of the obtained product was controlled by TLC technique using solvent system (ethyl acetate: acetone) in (9:1) ratio, R_f value (0.731), H^1-NMR (DMSO-d6) δ /ppm: 3.4 (s,2H,CH_2), 4.3 (s,1H,NH_2), 7.1-8.2 (m,H-aromatic) and 13 (s,1H,NH-triazole), FT-IR (KBr) υ /cm^{-1}: 3302 (NH_2), 3193 (NH), 1658 (C=O) and 1608 (C=N), UV (methanol) λ_{max} : 290 and 254 nm.

Synthesis of ethyl 5-(2-(α-phenylacetyl)phenyl)-4H-1,2,4-triazol-3-yl carbamate (3): (Aly and EL-Sayed, 2006)

Ethyl chloroformate (0.023 mole, 2.2 ml) was added dropwise to a solution of compound (2) (0.023 mole, 6 gm) in pyridine (15 ml). The reaction mixture was stirred at room temperature for (1 hr.), it was then poured on (100 ml) ice-water and the precipitated carbamate was filtered off, washed thoroughly with water, dilute hydrochloric acid then water again and recrystallized from ethanol to afford compound (3), (4.6 gm), m.p. (148-150°C) in (61%) yield. The purity of the obtained product was controlled by TLC technique using solvent system (ethyl acetate: acetone) in (9:1) ratio, R_f value (0.773), H^1-NMR (DMSO-d6) δ /ppm: 1.4 (t,3H,CH_3), 3.4 (s,2H,CH_2), 4.5 (q,2H,O-CH_2), 7.1-8.3 (m,H-aromatic), 8.4 (s,1H,NH) and 13 (NH-triazole), FT-IR (KBr) υ / cm^{-1}: 3159 (NH), 1763 (C=O urethane), 1658 (C=O ketone) and 1608 (C=N), UV (methanol) λ_{max} : 238 and 282 nm.

Synthesis of 4-(5-(2-(α-phenylacetyl)phenyl)-4H-1,2,4-triazol-3-yl) semicarbazide (4): (Mayekar, 2010)

A mixture of appropriate carbamate (3) (0.01 mole, 3.32 gm) and excess of hydrazine hydrate (80%) (0.08 mole, 4 ml) in ethanol (30 ml) with a catalytic amount of triethyl amine (1ml). The reaction mixture was stirred for (3 hrs.) then poured on ice-water and acidified with diluted hydrochloric acid. The precipitate that formed was filtered off, washed thoroughly with water, dried to give compound (4) (2.9 gm), m.p. (194-196°C) in (91%) yield. The purity of the obtained product was controlled by TLC technique using solvent system (ethyl acetate: acetone) in (9:1) ratio, R_f value (0.714), H^1-NMR (DMSO-d6) δ /ppm: 3.4 (s,H,NH_2), 4.3 (s,2H,CH_2), 6.9 (s,1H,NH-urea), 7.1-8.2(m,H-aromatic) and 13.2 (s,1H,NH-triazole), FT-IR (KBr) υ /cm^{-1}: 3300 (NH_2), 3159 (NH), 1690 (C=O ketone), 1658 (C=O amide) and 1608 (C=N), UV (methanol) λ_{max} : 246 and 274 nm.

Synthesis of 2-phenyl-1-(2-(5-(5-aryl-1,3,4-oxadiazol-2-ylamino)-4H-1,2,4-triazol-3-yl)phenyl)ethanone (5a-f): (Revanasiddappa and Subrahmanyam, 2010)

A mixture of compound (4) (0.0005 mole, 0.16 gm), substituted benzoic acid (0.0005 mole) and phosphorous oxychloride (3 ml) was refluxed for (4 hrs.). The contents were cooled to room temperature and poured onto crushed ice. It was then neutralized by adding sodium bicarbonate. The solid product was collected by filtration then dried. Further purification was done by recrystallization from a mixture of methanol-water to yield the desired oxadiazoles (5a-f). The purity of the obtained product was controlled by TLC technique using solvent system (ethyl acetate: acetone) in (9:1) ratio. The physical and spectral data were listed in Table (1) and (2).

Table 1: Physical properties and spectral data for compounds (5a-f).

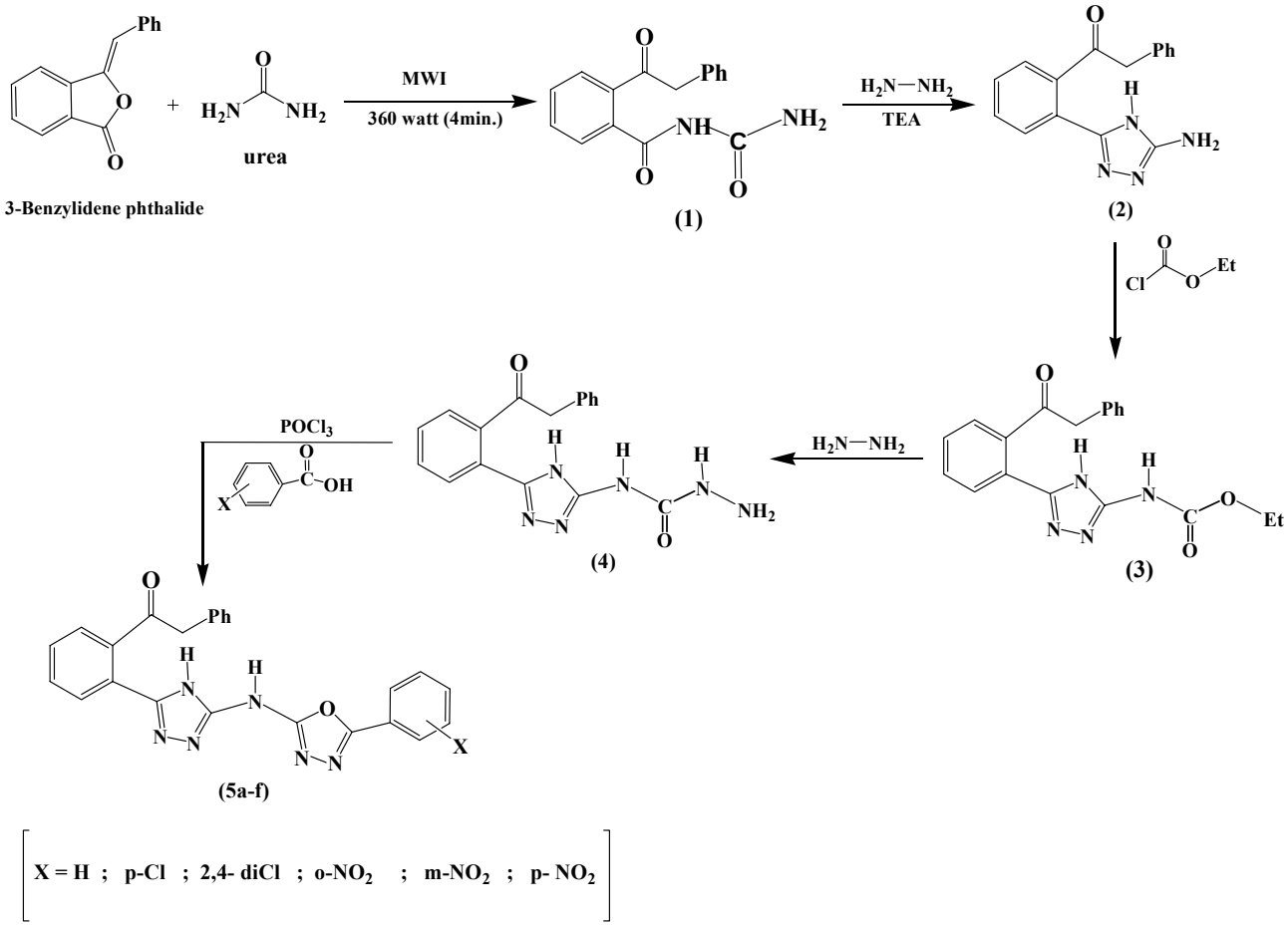
Comp. No.	X	M.P. (°C)	Yield (%)	R_f Value	UV (MeOH) λ_{max} (nm)	IR (KBr) υ (cm^{-1})				
						NH	C=O	C=N	C-O-C (cyclic)	others
5a	H	140-142	65	0.487	280	3162	1660	1599	1169	—
5b	o-Cl	127-129	62	0.407	278	3170	1655	1591	1174	—
5c	2,4-diCl	98-101	68	0.438	280	3161	1658	1608	1180	—
5d	o-NO_2	206-208	81	0.628	274	3171	1664	1604	1166	NO_2 asym 1545 sym 1321
5e	m-NO_2	140-141	72	0.608	278	3163	1658	1608	1173	NO_2 asym 1535 sym 1392
5f	p-NO_2	122-123	67	0.452	282	3163	1660	1601	1174	NO_2 asym 1522 sym 1390

Table 2: The H^1-NMR spectral data for compounds (5a-c and 5e-f).

Comp. No.	X	H^1-NMR (DMSO-d_6) δ (ppm)
5a	H	4.4 (s,2H,CH_2), 4.9 (s,1H,NH), 7.1-8.5 (m,H-aromatic) and 13.2 (s,1H,NH-triazole)
5b	o-Cl	3.4 (s,2H,CH_2), 4.8 (s,1H,NH), 7.1-8.4 (m,H-aromatic) and 13.0 (s,1H,NH-triazole
5c	2,4-diCl	4.2 (s,2H,CH_2), 4.7 (s,1H,NH), 7.2-8.4 (m,H-aromatic) and 12.9 (s,1H,NH-triazole
5e	m- NO_2	3.9 (s,2H,CH_2), 4.9 (s,1H,NH), 7.2-8.6 (m,H-aromatic) and 12.8 (s,1H,NH-triazole
5f	p- NO_2	3.8 (s,2H,CH_2), 4.7 (s,1H,NH), 7.2-8.4 (m,H-aromatic) and 12.9 (s,1H,NH-triazole

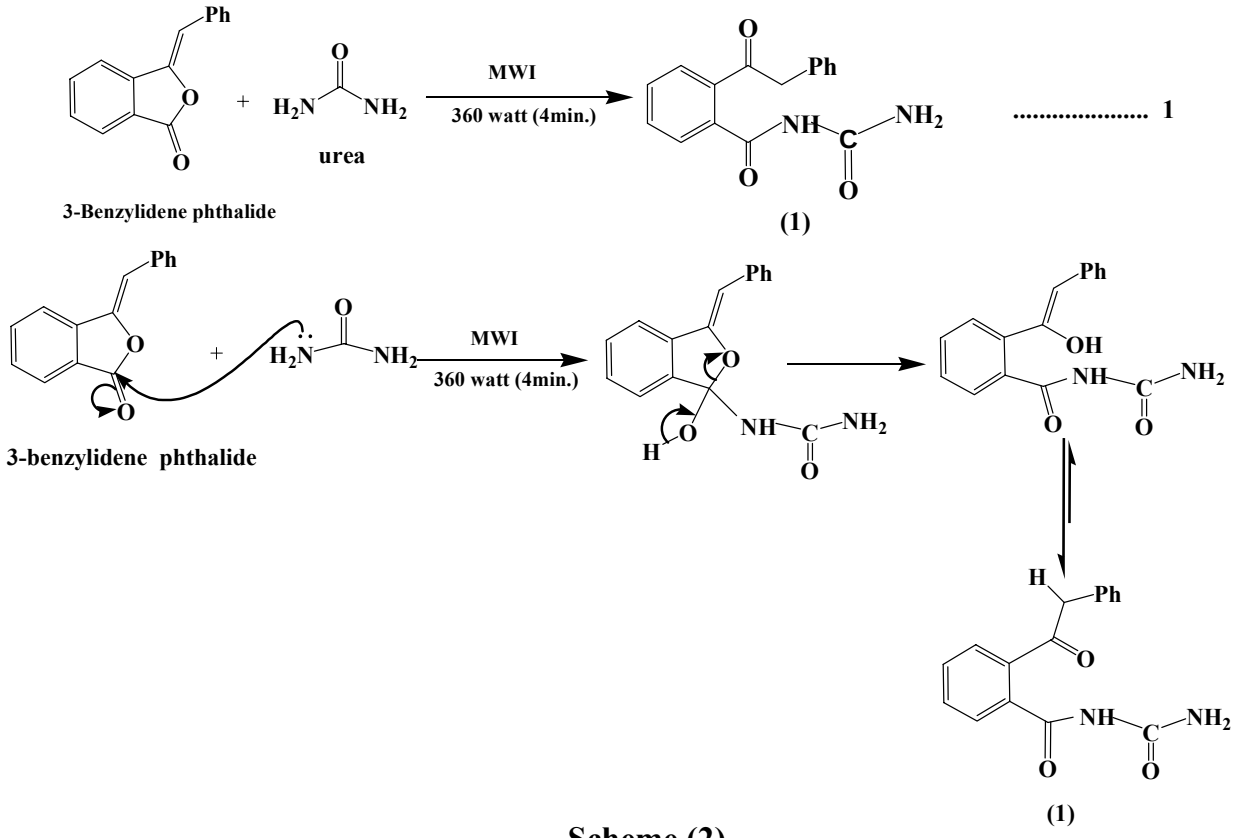
RESULTS AND DISCUSSION

The synthetic path way leading to the title compounds is given in scheme (1).



Scheme (1)

The synthesis of 2-phenyl-1-(2-(5-(5-aryl-1,3,4-oxadiazol-2-yl amino)-4H-1,2,4-triazol-3-yl)phenyl)ethanone (5a-f) required in the first step preparation of the starting material, namely 1-(2-(α-phenylacetyl)benzoyl) urea (1) which was prepared from the direct reaction between (Z)-3-benzylidene phthalide as a useful precursor and urea. This reaction was found to proceed smoothly under microwave irradiation in dry conditions within (4 min.) at (360 watt) (equation 1), the proposed mechanism was summarized in scheme (2) (Chiriac *et al*., 2007; Youssef, 2006).

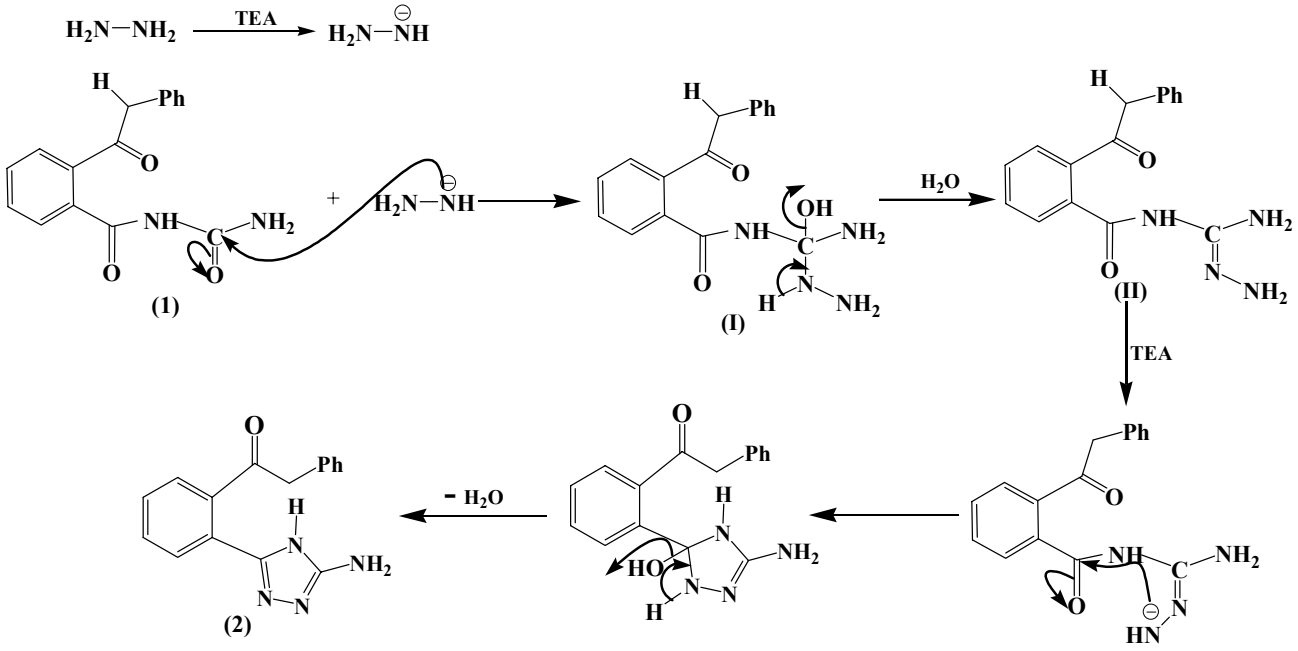


Scheme (2)

The structure of the later compound was established on the bases of the presence of an (NH_2) and (NH) absorption bands in the (3205 cm^{-1}) and (3163 cm^{-1}) region, (C=O) ketone and amide absorption bands at (1677 cm^{-1}) and (1657 cm^{-1}) region respectively in it's IR spectrum, whereas it's UV spectrum revealed the presence of absorption band at λ_{max} (226 nm) due to the conjugation, (Finar, 1977; Parikh, 1974). Further structure proof of compound (1) has came from ^{1}H-NMR spectra which showed significant peaks at δ (ppm): 3.5 (s,2H,CH_2), 6.7 (s,2H,NH_2), 7.1-8.2 (m,H-aromatic) and 10.67 (s,1H,NH).

Compound (1) reacted with hydrazine hydrate (80%) through cycloaddition reaction in refluxed ethanol to obtaine compound (2) represented by 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone. The mechanism of this reaction proceed through an ordinary

nucleophilic attack of hydrazine hydrate the amide carbonyl carbon to afford the intermediat (I) which in turn loses a molecule of water to give the condensed intermediat (II). The other NH_2 group of hydrazine will attack the other amide carbonyl carbon then the intramolecular cycloaddition reaction will occure to form compound (2). The mechanism of formation of compound (2) is outlined in scheme (3) (Aly *et al*., 2009; Shetgiri and Nayak, 2005; Al-Mousawi and El-Apasery, 2009).

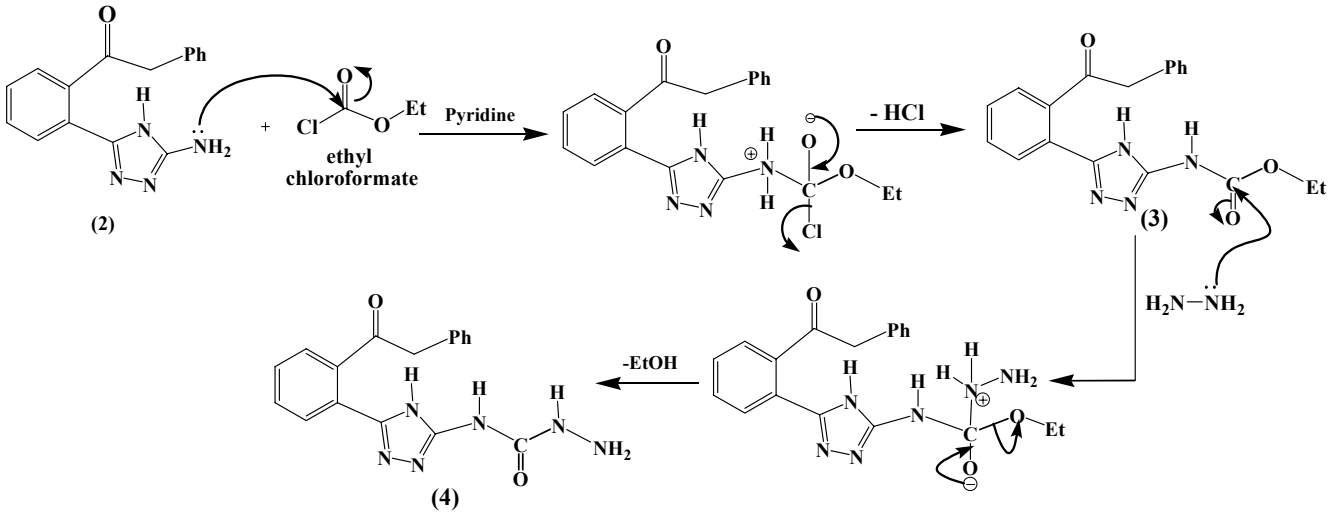


Scheme (3)

The structure of compound (2) was confirmed by IR and UV spectra. The IR spectrum shows a characteristic absorption band at: (3302 cm^{-1}) corresponding to (NH_2) functional group, (3193 cm^{-1}) corresponding to (NH) functional group, (1658 cm^{-1}) releated to (C=O) functional group and (1608 cm^{-1}) assigned to (C=N) functional group. The absence of both (C=O) of amide gave an evidence for the formation of compound (2), while it's UV spectrum showed absorption band at λ_{max} (290 nm) and (254 nm) due to the increasing of ring system and also to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition respectively, (Finar, 1977; Parikh, 1974). On the other hand, the structure of compound (2) was confirmed by ^{1}H-NMR spectra which showed significant peaks at δ (ppm): 3.4 (s,2H,CH_2), 4.3 (s,2H,NH_2), 7.5-8.2 (m,H-aromatic) and 13.0 (s,1H,NH-triazole).

Compound (2) was also underwent nucleophilic substitution reaction with ethyl chloroformate to afford the corresponding ethyl 5-(2-(α-phenylacetyl)phenyl)-4H-1,2,4-triazol-3-yl carbamate (3), which in turn reacted with hydrazine hydrate to give the corresponding

4-(5-(2-(α-phenylacetyl)phenyl)-4H-1,2,4-triazol-3-yl)semicarbazide (4), Scheme (4) outlined the synthesis of compounds (3) and (4) respectively, (Demirbas *et al*., 2005; Loudon, 2002).

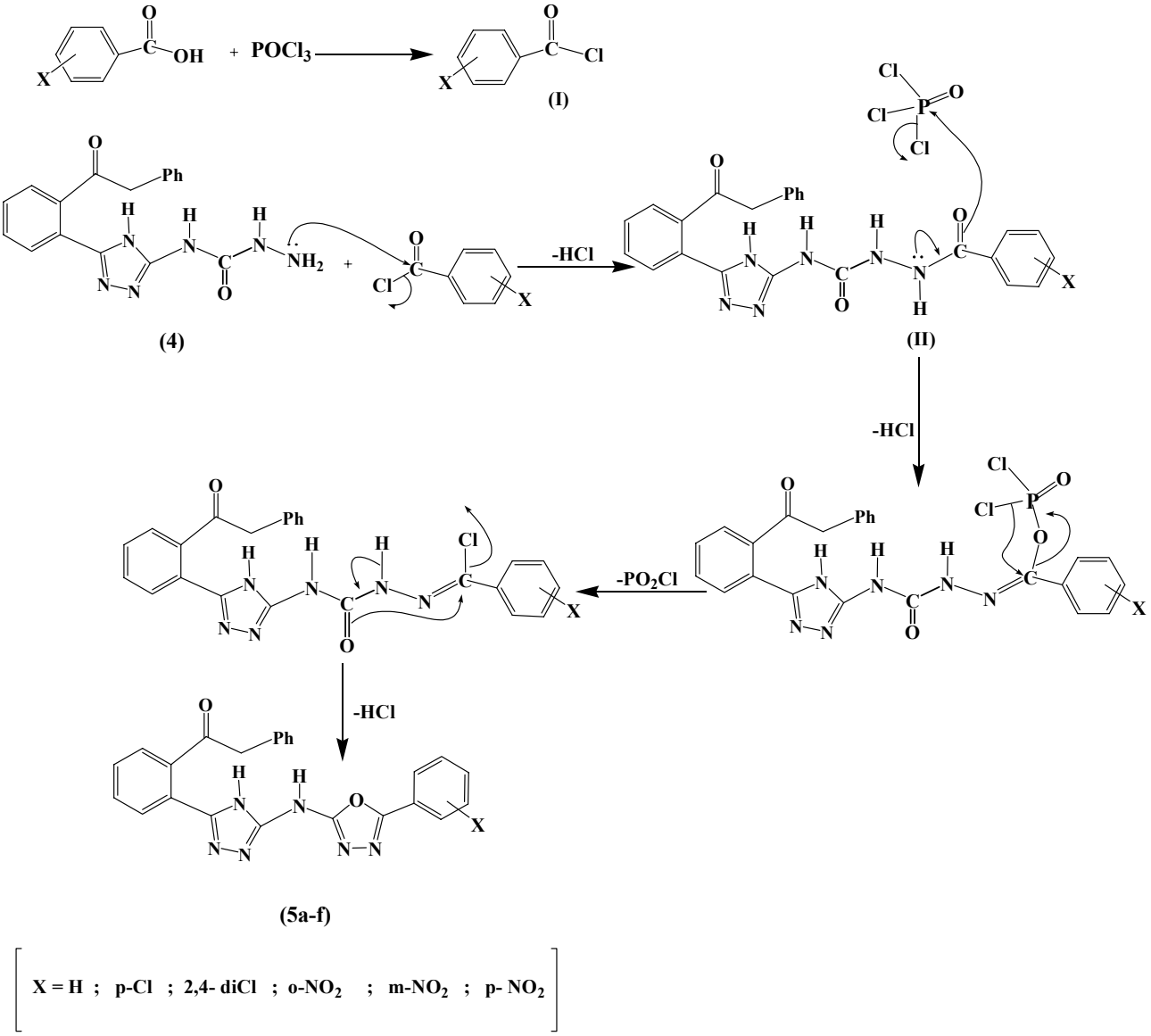


Scheme (4)

The spectral analysis represented by (IR and UV) spectra support the proposed structures of compounds (3) and (4). The IR spectrum of compound (3) showed absorption bands at (3159 cm^{-1}), (1763 cm^{-1}), (1658 cm^{-1}) and (1608 cm^{-1}) assigned to (NH), (C=O) urethane, (C=O) and (C=N) bond stretching respectively. While the spectrum of compound (4) showed absorption bands at (3300 cm^{-1}), (3159 cm^{-1}), (1690 cm^{-1}), (1658 cm^{-1}) and (1608 cm^{-1}) assigned to (NH_2), (NH), (C=O) urea, (C=O) and (C=N) bond stretching respectively. Moreover, the UV spectrum of compound (3) gave absorption band at λ_{max} (238 nm) and (288 nm) related to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transition respectively (Silverstein *et al*, 1974), whereas the UV spectrum of compound (4) gave absorption band at λ_{max} (246 nm) and (274 nm) attributed to the conjugation in the new synthesized system and also to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transition respectively, (Parikh, 1974; Silverstein *et al*, 1974). The ^{1}H-NMR measurement of compound (3) showed the following characteristic peaks at δ (ppm): 1.4 (t,3H,CH_3), 3.4 (s,2H,CH_2), 4.5 (q,2H,O-CH_2), 7.1-8.3 (m,H-aromatic), 8.4 (s,1H,NH) and 13 (NH-triazole), while compound (4) showed absoption peaks at δ (ppm): 3.4 (s,2H,NH_2), 4.3 (s,2H,CH_2), 6.9 (s,1H,NH-urea), 7.1-8.2 (m,H-aromatic) and 13.2 (s,1H,NH-triazole).

In order to prepare and characterize the final products represented by compounds (5a-f), compound (4) can be considered as useful intermediat, it was treated with different substituted benzoic acid in presence of phosphorous oxychloride which act as a chlorinating and dehydrating agent respectively. Mechanistically, it is reasonable to assume that the reaction was proceeded firstly via chlorination of substituted benzoic acid to afford the acid chloride intermediate (I) which upon reaction with compound (4) yielded the semicarbazide intermediate (II). Finally, cyclodehydration of the intermediate (II) takes place in the presnce of

phosphorous oxychloride yielded the corresponding compounds (5a-f) as shown in scheme (5), (Said, 2006).



Scheme (5)

The structure of compounds (5a-f) were elucidated in the basis of their spectral data which was came in agreement with the proposed structure, Table (1 and 2). Thus, in IR spectra the absence of bands due to (C=O urea) and (NH_2) bond stretching which are present in the parent compound (4) and the presence of bands due to cyclic (C-O-C) and only (N-H) sharp band at (1166-1180 cm^{-1}) and (3161-3171 cm^{-1}) bond stretching respectively, clearly indicated the

formation of compounds (5a-f). On the other hand, in UV spectra they showed maximum absorption bands at λ_{max} (274-282 nm) related to the resonance effect (Parikh, 1974; Finar, 1977). The ^{1}H-NMR measurement of compound (5a-c and 5e-f) are in agreement with the proposed structure, Table (2). The proton of 1,2,4-triazole ring appear as singlet peak at (13.2-12.9 ppm), whereas the aromatic protons appears as multiplet in the region between (7.1-8.6 ppm). The peaks of the NH and CH_2 protons appear as singlet at (4.9-4.7 ppm) and (4.4-3.4 ppm) respectively.

The purity of the synthesized 1,3,4-oxadiazoles (5a-f) were ascertained by thin layer chromatography (TLC) using (ethyl acetate: acetone) (9:1) ratio as suitable solvent system (Khan *et al*., 2004). This technique was also used to provide the formation of compounds (5a-f) by comparing it's R_f values with those of compound (4), Table (1).

REFERENCES

Al-Mousawi, S. M.; El-Apasery, M. A. (2009). Azolyacetones as precursors to indoles and naphthofurans facilitated by microwave irradiation with simultaneous cooling, *Molecules*, **14**, 2976-2984.

Aly, A.A.; EL-Sayed, R. (2006). Synthesis and biological activity of new 1,3,4-thiadiazole derivatives,*Chem. Pap.,* **60** (1), 56-60.

Aly, A.A.; Brown, A.B.; El-Emary, T.I.; Ewas, A.M.M.; Ramadan, M. (2009). Hydrazine carbothioamide group in the synthesis of heterocycles, *ARKIVOC*, **I**, 150-197.

Arulmurugan, S.; Kavitha, H. P. (2010). 2-Methyl-3-{4-[2-(1*H*-tetrazol-5-yl)ethylamino] phenyl}-3*H*-quinazolin-4-one, *Molbank*, **M695**,1-5.

Awadallah, A.M. (2006). Reaction of aryl- and heteroaryl benzoyl- and acetyl hydrazones with phenylisocynate synthesis of substituted -2,3-dihydro-1,3,4-oxadiazoles, *The Islamic University J. (Series of Natural Studies and Engineering)*, **14**(1), 129-133.

Banday, M.R.; Mattoo, R.H.; Rauf, A. (2010). Synthesis, characterization and antibacterial activity of 5-(alkenyl)-2-amino- and 2-(alkenyl)-5-phenyl-1,3,4-oxadiazoles, *J. Chem. Sci.*, **122**(2), 177-182.

Bari, S.B.; Agrawal, A.O.; Patil, U.K. (2008). Synthesis and pharmacological evaluation of some novel isatin derivatives for antimicrobial activity, *J. Sci. Islamic Republic of Iran*, **19**(3), 217-221.

Benjamin, E.; Hijji, Y. (2007). A novel microwave synthesis of unsubstituted cyclic imides, *11th International Electronic Conference on Synthetic Organic Chemistry*.

Caiazzo, A.; Dalili, S.; Picard, C.; Sasaki, M.; Siu, T.; Yudin, A.K. (2004). New methods for the synthesis of heterocyclic compounds, *Pure Appl. Chem.*, **76**(3), 603-613.

Chiriac, C.I.; Nechifor, M.; Tanasa, F. (2007). Formamide, a novel challenging reagent for the direct synthesis of non-substituted cyclic imides, *Revue Roumaine de Chimie*, **52**(8- 9), 883-886.

Conner, D.E. (1982). Benzalphthalides and broad spectrum sun screen, *U.S. Patent*, **4,**333,920.

Dalloul, H. M. (2010). Heterocyclic synthesis using nitrilimines: part 14.synthesis of new pyrazole derivatives, *Turk J. Chem.*, **34**, 529-535.

Del olmo, E.; Barboza, B.; Ybarra, M. I.; Lo´pez-Pe´rez, J. L.; Carro´n, R.; Sevilla, M.A.; Bosellid, C.; Felicia, A.S. (2006). Vasorelaxant activity of phthalazinones and related compounds, *Bioorganic and Medicinal Chemistry Letters*, **16**, 2786–2790.

Dewangan, D.; Pandey, A.; Sivakumar, T.; Rajavel, R. (2010). Synthesis of some novel 2,5-disubstituted 1,3,4-oxadiazole and its analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activity, *International J. Chem. Tech. Research*, **2**(3), 1397-1412.

Finar, I.L. (1977). "Organic Chemistry". Longman, Vol. 2, pp.17-18.

Ganji, S.H.; Karigar, C.S.; Pujar, B.G. (1993). Metabolism of benzalphthalide by Pseudomonas sp, *World Journal of Microbiology and Biotechnology* , **9**, 597-598.

He, D.; Zhu, Y.; Yang, Z.; Hu, A.; Cao, G. (2009). Synthesis, characterization, and optical properties of novel 2,5-bis[4-(2-(aryl vinyl)phenyl]-1,3,4-oxadiazoles, *Turk. Chem.*, **33**, 393-397.

Hrnčiar, P.; Ertl, P.; Hrnčiar, P.; Toma, Š. (1994). Complexation of phthalides and substituted 3-benzylidene phthalides with $Cr(CO)_6$, *J. Organometallic Chem.*, **464** (1), 65-69.

Humber, L.G. (1974). 5-Cycloalkylidene dibenzocycloheptene derivatives, *U.S. Patent*, **3,** 832,405.

Husain, A.; Ajmal, M. (2009). Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties, *Acta. Pharm.*, **59**, 223-233.

Ibrahim, T.M. (1991). Synthesis of biological active 3- benzylidenephthalide derivatives, *Arch. Pham. Res.*, **14**(4), 342-345.

Ilango, K.; Valentina, P.; Umarani, N.; Beena, K.P. (2010). Eco-benign mediated versatile synthesis of newer quinazolin-4- (3H)-one clubbed isatin derivatives as potent antimicro-bial agents, *Int. J. Res. Pharm. Sci.*, **1**(2), 133-138.

Jain, N.; Pathak, D.P.; Mishra, P.; Jain, S. (2009). Syntheses and antibacterial studies of some 2-[5-(aryl)-[1,3,4]oxadiazole-2-ylsulfanyl] alkanoic acids, *J. Iran. Chem. Soc.*, **6**(1), 77-81.

Kanazawa, C.; Terada, M. (2007). Organic-base-catalyzed synthesis of phthalides via highly regioselective intramolecular cyclization reaction, *Tetrahedron Lett.*, **48**(6), 933-935.

Khan, K.M.; Ullaha, Z.; Rania, M.; Perveenb, S.; Haidera, S.M.; Choudharya, M.I.; Rahmana , A.; Voelter, W. (2004). Microwave-assisted synthesis of 2,5-disubstituted-1,3,4-oxadiazoles, *Letters in Organic Chemistry*, **1**, 50-52.

Kim, H.S.; Kang, S.M. (2008). Facile synthesis and characterization of poly (dialkoxy-p-phenylene-1,3,4-oxadiazole-*alt*-phenylene-1,3,4-oxadiazoles), *Macromolecular Research*, **16**(4), 360-366.

Kundu, N.G.; Pal, M.; Nandi, B. (1998). Palladium-catalysed heteroannulation with terminal alkynes: synthesis of phthalides, *J. Chem. Soc., Perkin Trans.*, **1**, 561-568.

Kurume, A.; Kamata, Y.; Yamashita, M.; Wang, Q.; Matsuda, H.; Yoshikawa, M.; Kawasaki, I.; Ohta, S. (2008). Synthesis of 3-substituted isocoumarins and their inhibitory effects on degranulation of RBL-2H3 cells induced by antigen, *Chem. Pharm. Bull.*, **56**(9), 1264- 1269.

Litvan, F.; Stoll, W. (1958). Substituted 2-phenyl indan-1,3-dione, *U.S. Patent*, **2,** 820,738.

Mayekar, A.N. (2010). Synthesis and antimicrobial studies on new substituted 1,3,4-oxadiazole derivatives bearing 6-bromonaphthalene moiety, *Int. J. Chem.*, **2**(1), 38-54.

Mitsui, Y.; Aoki, Y. (2010). In vitro effect of current antimalarial drugs on the survival of paired Schistosoma mansoni adult worms and their egg production, *Tropical Medicine and Health*, **38** (2), 69-73.

Mostafa, T.B. (2010). Synthesis and modification of some heterocyclic compounds with potential biological activity coupled on poly (maleic anhydride –methyl methacrylate), *J. Amer. Sci.*, **6**(8), 515-524.

Naik, R.; Naik, H.S.B.; Kumar, H.N.H.; Hosamani, K.M.; Mahadevan, K.M. (2009). Studies on the synthesis and fluorescent properties of long-chained 2-(5-alkyl-1,3,4-oxadiazole-2-yl)-3*H*-benzo[*f*]chromen-3-ones, *ARKIVOC*, **II**, 11-19.

Narasimhan, B.; Kumar, P.; Sharma, D. (2010). Biological activities of hydrazide derivatives in the new millennium, *Acta. Pharmaceutica Sciencia* , **52**, 169-180.

Parikh, V.M. (1974). "Absorption Spectroscopy of Organic Molecules". Edition Wesely Publishing Comp., Inc., 30p.

Patel, N.B.; Patel, J.C. (2010). Synthesis and antimicrobial activity of 3-(1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-ones, *Sci. Pharm.*, **78**, 171–193.

Patil, S.T.; Karink A.V.(2007). Cascade synthesis of racemic 3-aryl phthalid, *Indian J. Chem.* **46B**, 710-712.

Phan, D.H.T.; Kim, B.; Dong, V. M.(2009). Phthalides by rhodium-catalyzed ketone hydroacylation, *J. Amer. Chem. Soc.*, **131**, 15608–15609.

Revanasiddappa, B.C.; Subrahmanyam, E.V.S. (2010). Synthesis and biological evaluation of 2, 5-disubstituted-1, 3, 4-oxadiazoles, *Int. J. Chem. Tech. Res.* , **2**(2), 1094-1096.

Rios, M.Y.; Delgado, G. (1999). Lewis acid catalyzed transformations Z-ligustilide, *J. Mexican Chem. Soc.*, **43**(3,4), 127-32.

Rosenthal, A.; Yalpani, M. (1965). Reaction of aralkyl ketone phenylhydrazones with carbon monoxide; thermal indolization of aralkyl ketone phenylhydrazones, *Canadian J. Chem.*, **43**, 3449-3451.

Said, S.A. (2006). Synthesis of some new 2-(2-isopropyl-5-methyl phenoxymethyl)-5-aryl-1,3,4-oxadiazoles, *Raf. J. Sci.*, **17**(4), 52-58.

Scholl, T.; Serini, V.; Rathmann, D.; Savage, R.; Kircher, K. (1989). Use of 3-benzalphthalide as uv stabilizers for thermoplastic, aromatic polyesters, polycarbonates and polyester carbonates, *U.S. Patent*, **4,797,435**.

Şener, A. (2004). One step synthesis and some reactions of 7-hydrazino-3,4-diphenyl-2*H*-pyrazolo [3,4-d]pyridazine, *Turk. J. Chem.*, **28**, 39 - 45.

Sharma, R.K.; Shrivastava, K.; Daniel, V.; panwar, M. S.; Goyal, S. (2010). Synthesis and anti helmentic activity of some azole derivatives of hippuric acid, *Int. J. Pham. Sci.,* **2**(2), 502-507.

Shetgiri, N.P.; Nayak, B.N. (2005). Synthesis and antimicrobial activities of oxadiazoles, phthalazines and indolinones, *Indian J. Chem.*, **44B**, 1267-1272.

Shibata, T.; Gaesser, G. (1991). Sensitizer for heat paper coatings, *U.S. Patent*, **5,** 066,633.

Silverstein, R.M.; Bssler, C.G.; Morril T.C. (1974). " Spectrometric Identification of Organic Compounds ", 3rd edn., John Wiley and Sons, Inc., pp. 246-247.

Srinivas, K.; Kumar, K.P. (2010). Synthesis, antimicrobial and antihelmintic activity of 1-[(5-substituted-1,3,4-oxadiazole-2-yl)methyl]-4-propylpiperazines, *International J. Biopharmaceu.*, **1**, 14-19.

Tang, Y.; Zhu, M.; Yu, S.; Hua, Y.; Duan, J.; Su, S.; Zhang, X.; Lu, Y.; Ding, A. (2010). Identification and comparative quantification of bio-active palides in essential oils from si-wu-tang, fo-shou-san, radix angelica and rhizoma chuanxiong, *Molecules*, **15**, 341-351.

Viña, D. ; del Olmo, E.; Lopez-Pérez, J. L.; Feliciano, A.S. (2008). Pyrazolo[3,4,5-*de*] phal--azine. Syntheses of a practically unknown heterocyclic system, *Tetrahedron*, **65**(8), 1574-1580.

Youssef, A.S.A. (2006). Reactions of 3-substituted-5-arylmethylene-1,3-thiazolidin-2,4-diones with azide and cyanide ions, *World J. Chem.*, **1** (1), 10-19.