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Synthesis of Some New 1,3,5-Oxadiazine Derivatives

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ABSTRACT

Some new derivatives of 1,3,5-oxadiazine-4-one (7-9) and 1,3,5-oxadiazine-4-thione (10-12) were synthesized using two different diamides (N, N′-Diaroyl urea /thiourea Compounds (1-6)).

N, N′-Diaroyl urea /thiourea compounds (1-6) were prepared by the reaction of urea and thiourea with benzoyl chloride and substituted benzoyl chloride respectively under basic conditions. Cyclodehydration of the diamides under acidic conditions afforded the 1,3,5-oxadiazine compounds.

All compounds were identify by physical and spectroscopic methods.

Key words: Heterocyclics, Oxadiazine, Diamide.

تحضير عدد من مركبات 5,3,1- اوكسادايازين الجديدة

الملخص

تم تحضير عدد من معوضات 5,3,1- اوكسادايازين -4-اون (7-9) و5,3,1- اوكسادايازين-4- ثايون (10-12) باستخدام نوعين مختلفين من مركبات ثنائية الاميد (N,N′-ثنائي اروايل يوريا\ثايويوريـا (1-6)).

حضرت المركبات N, N′- ثنائي اروايل يوريا/ ثايويوريا (1-6) من مفاعلة اليوريا والثايويوريـا وكلوريد البنزويل (اومشتقاته) باستخدام ظروف قاعدية وقد عزلت هذه المركبات وتم ادخالها تفاعل حولقة بالسحب الضمني لجزيئة ماء باستخدام ظروف حامضية لتعطي مركبات 5,3,1- اوكسادايازين.

شخصت جميع المركبات المحضرة باستخدام الطرائق الفيزياوية والطيفية المتوفرة.

الكلمات المفتاحية: المركبات الحلقية غير المتجانسة، اوكسادايازين، ثنائية الاميد.

INTRODUCTION

Nitrogen containing heterocycles have received significant attention because of the unique physical and chemical properties of different heterocyclic compounds (Shafiee *et al.*, 1995). Six- membered heterocyclic ring with three hetero atoms are not found widely in the nature, but they have a superfine applications in the most important field (Katritzky and Rees,1984) such as medical (Stephen *et al.*, 2004), agriculture as insecticides (Bruno *et al.*, 2001; Ralf and Thomas, 2002) and in industry as adhesives (Takanen *et al.*, 2004). Oxadiazine compounds are considered to be a supreme type of this family since they are oxa-analogues of nucleosides-6-oxadihydro uracile (Katritzky and Rees, 1984). Therefore they show a significant application in biological field. Different methodes have been applied to synthesize 1,3,5-Oxadiazine compounds, some of them involving cycloaddition reaction between carbonyl compounds and heterodiene (Katritzky and Rees, 1984). The other method used the imidal compounds as good precursor to afford 1,3,5-oxadiazine compounds (Lin, 1975). On the other hand, isocynate compounds and its derivatives play apart in such synthesis (Otohiko *et al.*, 1966).

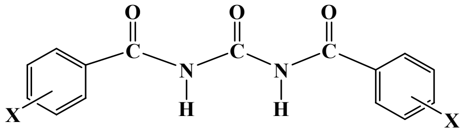
EXPERIMENTAL

Melting points (M.P) were measured on Electrothermal, 1A9300, Digital series (1998) melting point apparatus and are uncorrected. Infra-Red (FT-IR) spectra were recorded as (KBr) disc using a Bruker, FT-IR, spectrophotometer tensor 27. Proton-Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded using a Bruker-Avance, spectrophotometer 400 (H400MHz); with TMS as internal standard, and $CDCl_3$ and duterated DMSO as solvents; France, University of Réne Descartés. [(s) singlet; (d) doublet; (m) multiplet]. Ultra-Violet (U.V) spectra were performed on Shimadzu UV-Visible spectrophotometer UV-1650 PC using methanol as a solvent. Physical theoretical calculations and three dimentional (3D) configuration were pointed out using (Chem.Office) program, version 8.0.3 September 24, 2003, MOPAC/ MM_2.

A. Synthesis of N, N′-Diaroyl urea /thiourea compounds (1-6) (Takeo et al.,1958):

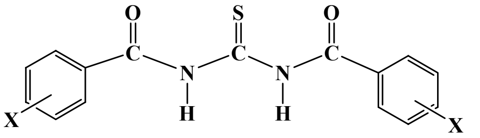
To a stirred solution of urea or thiourea (0.005mole) in dry benzene (30ml) pyridine (3ml) was added dropwise followed by slow addition of acid chloride (0.01mole). The suspension was stirred for about (1hr) and then refluxed for (3hrs). The reaction mixture was allowed to cool, the precipitate product was filtered off and washed with dry benzene then crystallized from n-butanol. (Table 1 and 2).

Table 1: Physical properties and spectral data of N,N′-diaroyl urea compounds (1-3)



Compd. No.	*X*	*Molecular Formula*	*M.P (°C)*	*Yield (%)*	*I.R (KBr) υ (cm^{-1})*				*U.V (MeOH) λ_{max} (nm)*
					N-H	*C=O conj.*	*C=O free*	*Others*	
1	**H**	$C_{15}H_{12}N_2O_3$	**263-264**	**56**	**3209**	**1644**	**1667**	—	**277**
2	**P-NO_2**	$C_{15}H_{10}N_4O_7$	**237-239**	**23**	**3194**	**1660**	**1681**	NO_2 asym1533 ; sym 1349	**265**
3	**3,5-DiNO_2**	$C_{15}H_8N_6O_{11}$	**254-255**	**99**	**3272**	**1621**	**1650**	NO_2 asym 1538; sym 1345	**260**

Table 2: Physical properties and spectral data of N,N′-diaroyl thiourea compounds (4-6)



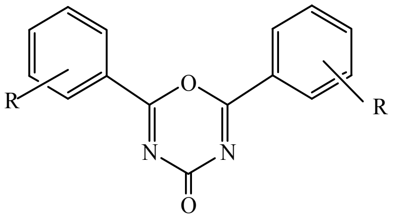
Compd. No.	*X*	*Molecular Formula*	*M.P (°C)*	*Yield (%)*	*I.R (KBr) υ (cm^{-1})*				*U.V (MeOH) λ_{max} (nm)*
					N-H	*C=S*	*C=O*	*Others*	
4	**H**	**$C_{15}H_{12}N_2O_2S$**	**260-262**	**79**	**3178**	**1171**	**1666**	**—**	**241**
5	**P-NO_2**	**$C_{15}H_{10}N_4O_6S$**	**89-90**	**30**	**3193**	**1170**	**1642**	**NO_2 asym1523 ; sym1319**	**265**
6	**3,5-DiNO_2**	**$C_{15}H_8N_6O_{10}S$**	**199 -201**	**48**	**3104**	**1171**	**1657**	**NO_2 asym1538 ; sym1344**	**254**

B. Synthesis of 2,6-diaryl-1,3,5-Oxadiazine -4-one(thione) (7-12):

General method (Finer,1977):

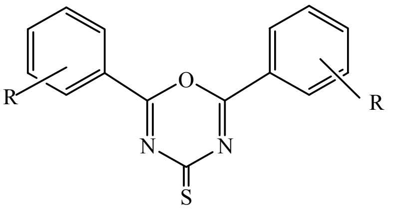
Acetic anhydride (5ml) was added to diamide (1-6) (0.0037mole). The reaction mixture was refluxed for (2hrs), then the mixture was allowed to cool and the precipitated product was collected by filteration and washed with pet-ether (60-80°C). The recrystallization of the crude product with absolute ethanol afforded the pure oxadiazines (7-12). Table (3 and 4).

Table 3: Physical properties and spectral data of 2,6-diaryl-1,3,5-oxadiazine -4-one compounds (7-9)



Compd. No.	*R*	*Molecular Formula*	*M.P (°C)*	*Yield (%)*	*I.R (KBr) υ (cm^{-1})*				*U.V (MeOH) λ_{max} (nm)*
					C=N	*C=O*	*C-O-C*	*Others*	
7	**H**	**$C_{15}H_{10}N_2O_2$**	**106-109**	**23**	**1581**	**1679**	**1282**	**—**	**241**
8	**P-NO_2**	**$C_{15}H_8N_4O_6$**	**240-243**	**17**	**1607**	**1695**	**1279**	**NO_2 asym1541 ; sym1312**	**241**
9	**3,5-DiNO_2**	**$C_{15}H_6N_6O_{10}$**	**191-193**	**13**	**1595**	**1687**	**1270**	**NO_2 asym1518; sym1345**	**243**

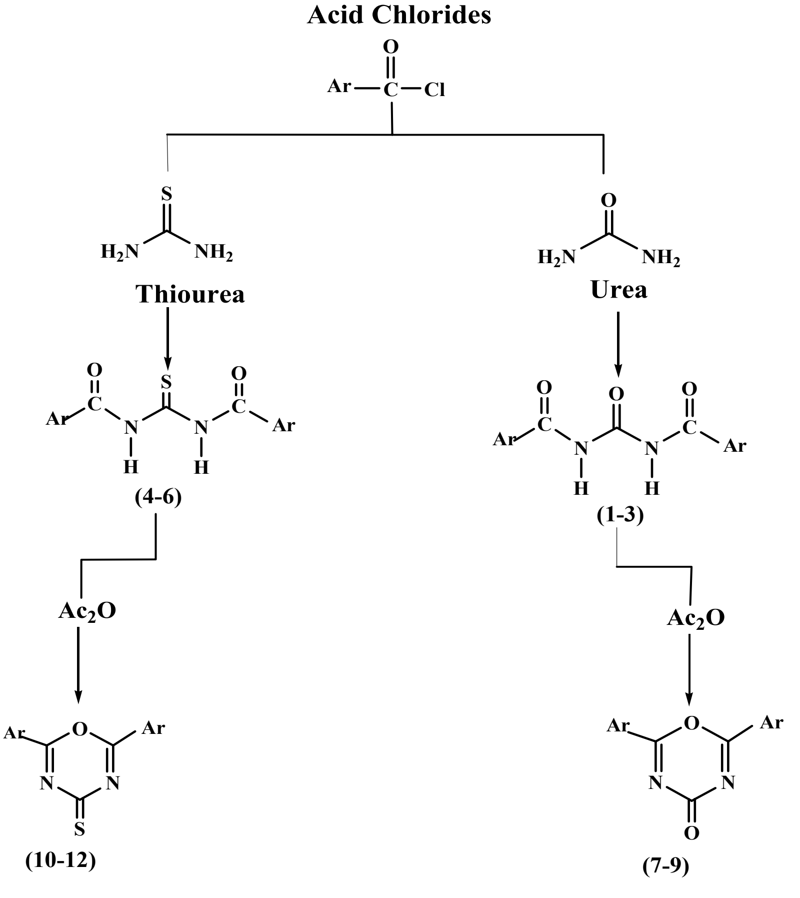
Table 4: Physical properties and spectral data of 2,6-diaryl-1,3,5-oxadiazine -4-thione compounds (10-12)



Compd. No.	***R***	***Molecular Formula***	***M.P (°C)***	***Yield (%)***	***I.R (KBr) υ (cm⁻¹)***				***U.V (MeOH) λmax (nm)***
					C=N	***C=S***	***C-O-C***	***Others***	
10	**H**	**$C_{15}H_{10}N_2OS$**	**258-259**	**55**	**1558**	**1171**	**1289**	**—**	**266**
11	**P-NO_2**	**$C_{15}H_8N_4O_5S$**	**191-194**	**18**	**1606**	**1174**	**1279**	**NO_2 asym 1541; sym 1311**	**236**
12	**3,5-DiNO_2**	**$C_{15}H_6N_6O_9S$**	**129-131**	**14**	**1626**	**1174**	**1270**	**NO_2 asym 1541; sym 1344**	**234**

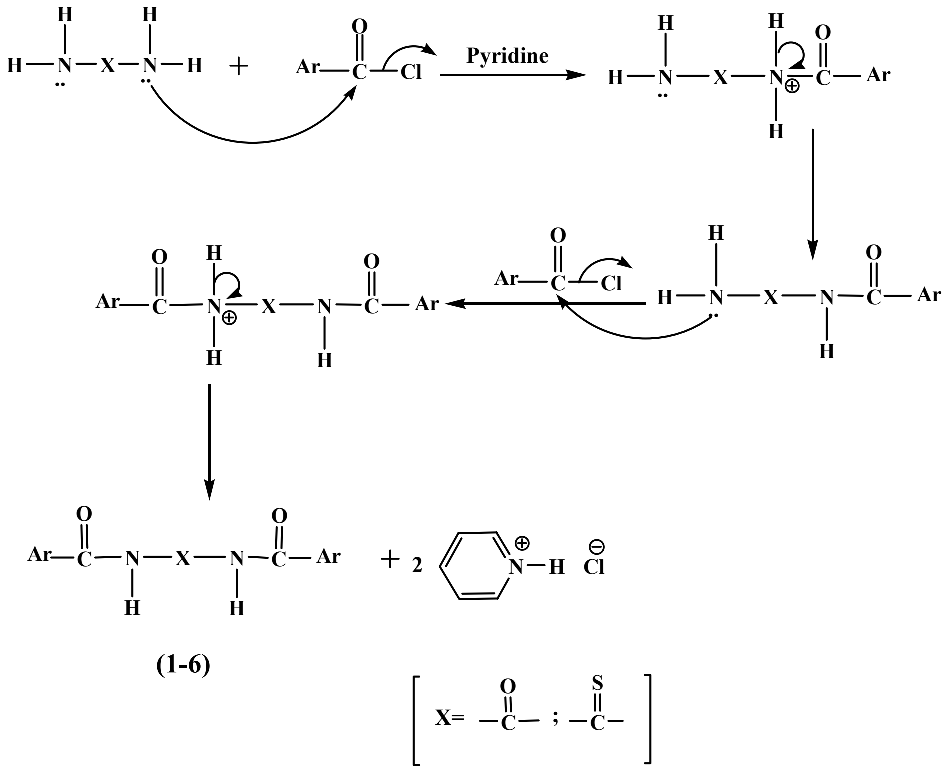
RESULTS AND DISCUSSION

Acid chlorides were found to be an important structural unite to construct a large number of organic compounds through their various reactions with different organic reagents. This promoted us to use these reactive intermediates as starting materials in the synthesis of some aromatic amides which then converted ultimately to new derivatives of six-membered heterocyclic compounds, as shown in scheme(1):-



Scheme (1)

Urea and thiourea represent an important nucleus for the synthesis of a large number of organic compounds through their reactions with different reagents (Finer, 1977 and Francis, 1996). Thus, the diamide compounds were synthesized by the reaction of urea and, thiourea with benzoyl chloride or substituted benzoyl chloride in the basic medium. The reaction proceeds through nucleophilic attack of the unshared pair of electron on the N-atom of the urea and thiourea to the carbonyl carbon atom of acid chloride to afford compounds (1-6) as shown in following mechanisum scheme (2):-



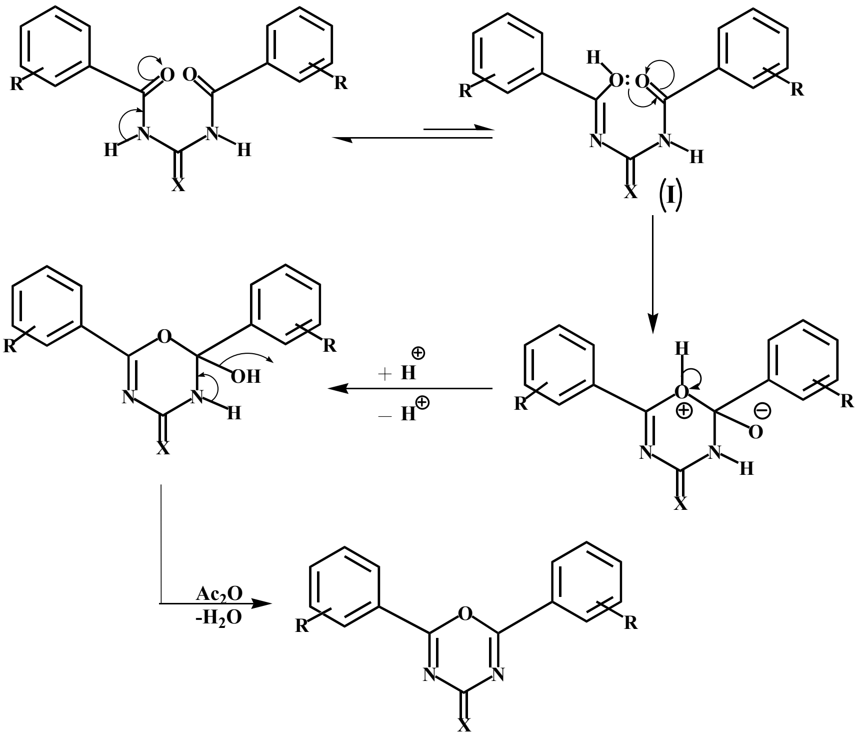
Scheme (2)

The compounds (1-6) serve as important precursors in the preparation of compounds containing oxadiazine ring system.The structure of the compounds (1-6) were confirmed by physical and spectral methods [Table 1 and 2] respectively, which came in good agreement with the suggested structures.

The I.R spectra for compounds (1-3) gave characterristic absorption bands at (3272-3194cm^{-1}) of (N-H) band streching, at (1681-1650cm^{-1}) for (C=O) free groups and at (1660 -1621cm^{-1}) for (C=O) conjugated group. The U.V spectra showed a shift in the λ_{max} toward higher wave length at (260-277nm) due to the resonance effect (Finer, 1977). Finally, the compound (1) was identified by ^{1}H-NMR spectrum which showed absorption peaks at δ 6.97(m, 4H,meta), δ 7.22-7.24(m, 2H,para), δ 8.0-8.02 (m,4H,ortho) and δ 10.92 (s,2NH).

On the other hand, the compounds (4-6) gave absorption bands at (3193-3104cm^{-1}) for (N-H) band streching, (1666-1642cm^{-1}) for (C=O) band streching and (1170-1171 cm^{-1}) for (C=S) band streching. We can see that there is a depression in the absorption frequencies of (N-H) and (C=O) groups due to the resonance effect (Parikh, 1974). For the same reason the U.V spectra showed a bathochromic shift at λ_{max} (241-265nm).

2,6-Diaryl-1,3,5-oxadiazine-4-one (thione) compounds (7-12) have been synthesized from N,N′-diaroyl urea or thiourea compounds (1-6), which is represented by 1,3,5-oxadiazine compounds (7-12). The reaction proceed through the formation of the iminole intermediate (I), which undergoes intracyclodehydration process by the action of acetic anhydride (Katritzky and Rees, 1984) to afford the oxadiazine derivatives (7-12), as shown in the following suggested mechanism scheme (3):-



(7-12)

[X= O (7-9) or S (10-12)] ; [R= H ; 4-NO_2 ; 3,5-di NO_2]

Scheme (3)

These compounds were identified by physical and spectral methods, [tables 3 and 4] respectively.

The I.R spectra for 2,6-Diaryl-1,3,5-oxadiazine-4-one compounds (7-9) showed absorption bands at (1695-1679cm^{-1}) assigned to the (C=O)band sterching ,at (1607-1581cm^{-1}) due to the (C=N) band sterching and at (1282-1270cm^{-1}) assigned to the (C-O-C) band sterching. The absence of (N-H) bands and the appearance of (C=N) and (C-O-C) bands gave an excellent support to the proposed products. The U.V spectra showed λ_{max} at lower wave length (241-243nm), which is caused by a ring strain (Finer, 1977).

On the other hand, the 2,6-diaryl-1,3,5-oxadiazine-4-thione compounds (10-12) showed characteristic absorption bands at (1626-1558cm^{-1}) assigned to the (C=N) band sterching, (1174-1171cm^{-1}) assigned to the (C=S) band sterching and at (1289-1270cm^{-1})

for (C-O-C) band sterching. The absence of both of (N-H) and (C=O) absorption frequencies and the appearance of both (C=N and C-O-C) absorption frequencies indicate the formation of the oxadiazine thione ring system. UV spectra showed a blue shift at λ_{max} (234-266nm) due to the loss of the two conjugated (C=O) groups , in addition to a ring strain (Finer, 1977). From structure activity relationship and drug design point of view, further structural information for compounds (9) and (12), as representative example, were obtained from the 3D-configurational structure as shown in Fig. (1) and Fig. (2), respectively. Heat of formation (H.F.) and steric energy (S.E.) for both compounds were calculated too. Discussion of the theoretical calculations is beyond the scope of this research.

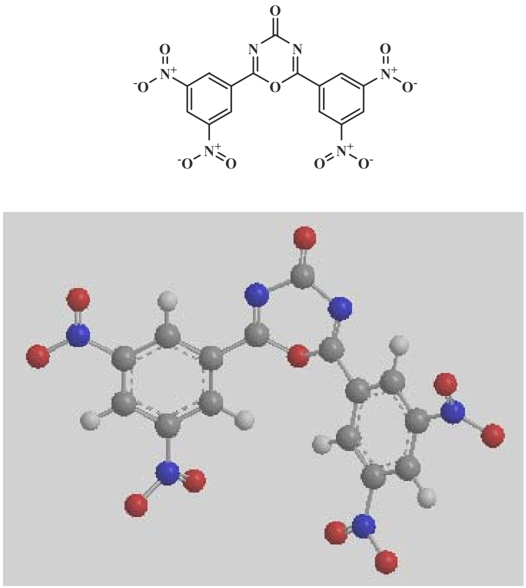


Fig. 1: 3D-structure of 2,6-bis (3,5-dinitro phenyi) 1,3,5-oxadiazine-4-one (9) Heat of Formation 81.8424 kcal/mole; Steric Energy -56.3723 kcal/mole

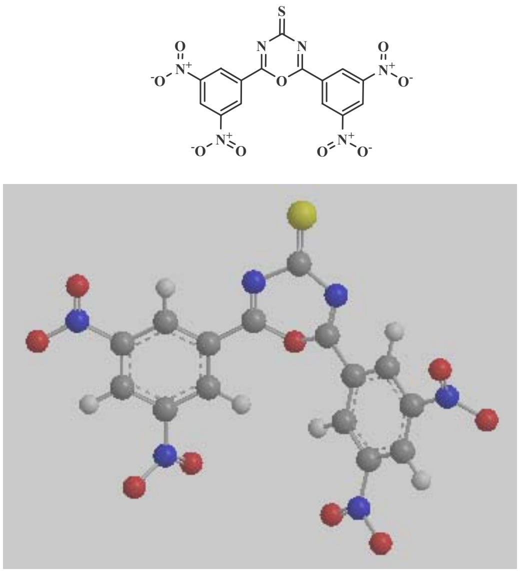


Fig. 2: 3D-structure of 2,6-bis (3,5-dinitro phenyi) 1,3,5-oxadiaz-4-thione (12) Heat of Formation 152.1027 kcal/mole; Steric Energy -65.0215 kcal/mole

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