

## Electrocyclization of Semicarbazone; A Novel Route of Green Synthesis of 2,5-Disubstituted-1,3,4-Oxadiazoles

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The anodic oxidation of a number of arylsemicarbazides derivatives (I) has been examined in acetonitril containing lithium perchlorate (LiClO<sub>4</sub>) as a supporting electrolyte (20g/l). The reaction was sensitive to the amount of electricity passed through the cell, so the electrode potential was determined on the basis of the oxidation potential of the compound which is measured by using the cyclic voltammetry. The electrochemistry reaction has been realised under controlled- potential because the constant current condition is necessary to carry the reaction in high selectivity. In this reaction condition the anodic oxidation of arylsemicarbazides derivatives (I) gives 2,5-disubstituted-1,3,4-oxadiazoles (II) as final compound.

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**Keywords:** Electrochemistry, oxadiazoles, anodic oxidation, cyclic voltametry, arylsemicarbazides

### 1. INTRODUCTION

Oxadiazoles belong to a group of heterocycles that have been attracting attention for last two decades due to their wide range of biological interactions.

The 1,3,4-oxadiazole ring system has been identified as the main core of many bioactive molecules. Compounds containing these aromatic five-membered heterocycles have been shown to exert anti-inflammatory [1], antimicrobial[2], anti-convulsant [3],and hypoglycaemic [4] hypoglycaemic [4] activities. In addition, 2,5-disubstituted-1,3,4-oxadiazoles are proposed to have potential agrochemical use [5] due to their wide spectrum of insecticidal [6] and acaricidal [7] properties attained by interfering with insect's chitin biosynthesis [8]. This class of materials also has gained the worth of modern applications such as scintillators, fluorescence and photographic materials

[9]. They are of interest as emitting layers in electroluminescent devices [10] and as structural units in polymeric membranes designed for gas separation applications [11]. Because of these interesting features several routes to the synthesis of 1,3,4-oxadiazoles have been developed. A majority of the 2,5-disubstituted-1,3,4-oxadiazoles have been synthesized from cyclodehydration of diacylhydrazines. This method of synthesis usually involves rigorous conditions or use of harsh reagents, e.g. POCl<sub>3</sub> [12], SOCl<sub>2</sub> [13], polyphosphoric acid [14], liquid sulfuric acid [15], phosphorus pentoxide [16], triflic anhydride [17], and BF<sub>3</sub>–OEt<sub>2</sub> [18]. Mild dehydrating agents like Burgess reagent [19] and carbodiimides are also used in this manner [20]. Another more popular route to the synthesis of 1,3,4-oxadiazoles is based on the preparation of acylhydrazones from unprotected acylhydrazines and aldehydes, followed by oxidation with a variety of oxidizing agents [21]. By a similar approach but in a non-oxidative media, trichloroacetylhydrazones gave 1,3,4-oxadiazoles through a formal oxidation of aldehyde-derived moiety of hydrazones [22]. To exclude the oxidation step, carboxylic acids have directly been used instead of aldehydes in the synthesis of 1,3,4-oxadiazoles via reaction with hydrazines [23]. Orthoesters are readily available carboxylic acid derivatives which react with acylhydrazines in milder and acid catalyzed conditions to afford 2,5-disubstituted-1,3,4-oxadiazoles [24]. However, many of these methods suffer from drawbacks such as long reaction times [25], unsatisfactory yields, special care in handling and storing the reagents, undesired side products in reaction with harsh reagents [26], using heavy metal oxidants [21], cumbersome product isolation procedure and environmental pollution. Therefore, a need still exists for further development of versatile and milder reaction conditions, using green and electro-organic reaction [27]. Many merits of the electro-organic synthesis [28] encouraged as to this method like: the electro organic reaction are achieved at room temperature, also since the polarity of a substrate is inverted by the transfer of electrons [29], the reaction between electrophile and electrophile or nucleophile and nucleophile, becomes possible. And finally the reaction scale is controlled easily and the electro-organic reactions are essentially non-polluting. The present work deals with the newly electro-synthesis, spectral characterization, of some 2,5-disubstituted-1,3,4-oxadiazoles.

## 2. EXPERIMENTAL PART

### 2.1. Apparatus and reagents:

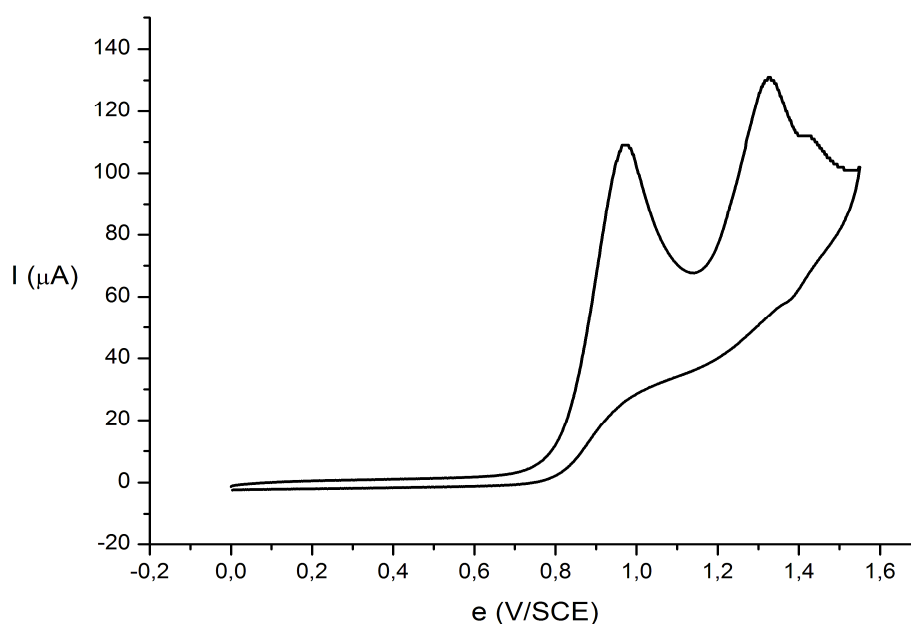
Cyclic voltammetry (CV) was performed in a model (PGZ 301) dynamic-EIS voltammetry with a traditional three-electrode system. All experiments were carried out in a conventional electrochemical cell, The electrode system contained a carbon paste working electrode (10.0cm in diameter) a platinum wire as counter electrode and saturated calomel as reference electrode. For the reagents and chemicals we used: Lithium perchlorate with the formula LiClO<sub>4</sub>, Benzaldehyde derivatives, semicarbazone hydrochloride all chemicals were reagent-grade materials, from Aldrich and E. Merck, respectively. These chemicals were used without further purification.

### 3. RESULTS AND DISCUSSION

#### 3.1. Voltammetric studies of 4-Methoxybenzaldehyde semicarbazone

Figure 1, shows the voltammetric curves obtained for the oxidation of 4-methoxybenzylidene) semicarbazide (I), the cyclic voltammogram of (I) shows two oxidation peak potentials at 0.9V and the second at 1.35V and no reduction peak potential (Figure 1)

It was recorded at a glassy electrode. Peak potentials are expressed in V/SCE and ohmic drop has not been corrected. The voltammograms of all the starting compounds are similar and so (E)-1-(4-methoxybenzylidene) semicarbazide Ia was selected as the model compound.



**Figure 1.** Cyclic voltammograms for (E)-1-(4-methoxybenzylidene) semicarbazide Ia

#### 3.2. Electrochemical Oxidation of 4-Methoxybenzaldehyde semicarbazone

##### 3.2.1. Electrode potential

The electrode potential has to be determined on the basis of the oxidation or reduction potential of the semicarbazide I which is measurable by using cyclic voltammetry, it's one of the most important factors in controlling the reaction to have a high selectivity.

From the voltammetric studies we see two peaks of oxidation each peak corresponds to the transfer of one electron, the controlled potential oxidation at the first peak will selectively lead to the one electron oxidation of the substrate, while the oxidation at the second peak potential will mainly bring about the reaction which is related with two-electron oxidation.

In the title reaction the potential is fixed at +0.9 V/SCE

### 3.2.2. Amount of electricity passed through the cell

The amount of electricity passed through the cell corresponds to the amount of one of the reagents in the usual chemical reaction. Theoretical amount of electricity can be calculated on the basis of the number of electrons which are required to promote the reaction; usually the unit used is coulomb or faraday per mol ( $F^{-1}\text{mol}$ ). In the constant current method, the current is kept constant throughout the reaction and hence the total amount of electricity is easily calculated by the following equation:

$$\text{Amount of electricity} = 96500 \times n \times M$$

Where  $H$  is the time in hours,  $A$  is the current amperes and  $M$  the amount of substrate in moles, for the title reaction the amount of electricity passed through the cell for 1g of compound is  $q = 1005,20$  (Q).

### 3.2.3. Temperature

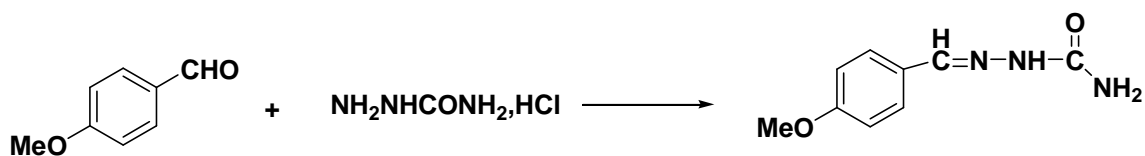
One of the most remarkable features of the most electro-organic reaction is that it is generally achievable at room temperature. As a matter of course the reaction temperature is not limited to room temperature; any temperature is allowed [30]. Often it's necessary to cool the cell externally due to heat evolution caused by the passage of electricity, in our reaction we just work at room temperature.

### 3.2.4. General producer of the electrochemical synthesis

#### 3.2.4.a) Synthesis of 4-Methoxybenzaldehyde semicarbazone Ia

Starting materials were synthesized according to known procedures [31] semicarbazide hydrochloride (0.68g, 63mmol) and freshly recrystallized sodium acetate (0.51g, 63mmol), were dissolved in water (10 ml) following a literature procedure. The reaction mixture was stirred at room temperature for 10 minutes. To this, 4-methoxybenzaldehyde (1g, 42mmol) was added and the mixture was shaken well. A little alcohol was added to dissolve the turbidity. The mixture was shaken for a further 10 minutes and allowed to stand.

The title compound (I) crystallizes on standing for 6 h. The separated crystals were filtered, washed with cold water and recrystallized from ethanol. Yield: 1g (84%).



**Scheme 1.** the synthesis of 4-Methoxybenzaldehyde semicarbazone

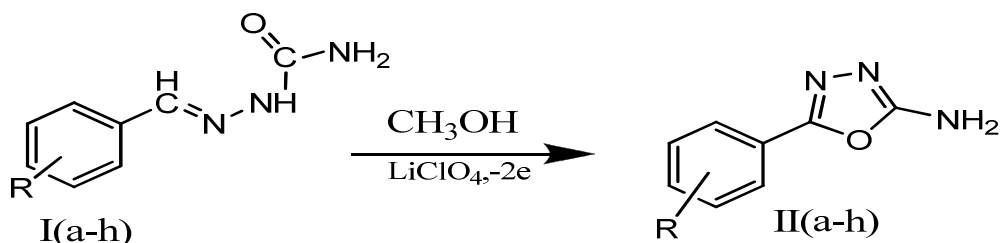
## 3.2.4.b) Electrochemical synthesis of 5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine IIb

The title reaction is carried out by using the technique of controlled potential electrolysis.

Before performing macroscale electrolyses, analytical investigation were carried out with a glassy carbon electrode at a scan rate of  $50\text{mV}^{-1}$ . The semicarbazide was dissolved in methanol containing lithium perchlorate ( $\text{LiClO}_4$ ) as a supporting electrolyte ( $20\text{g/l}$ ), this solution was placed in a non divided cell fitted with a glassy carbon electrode (diameter 10 cm) as anode electrode and a carbon rod as cathode two successive irreversible peaks (figure 1) were recorded at  $E_{pA} = 0.9\text{V/SCE}$  and  $E_{pB} = 1.35\text{V/SCE}$ .

These observations are consistent with previous results obtained in our laboratory and indicate that a selective bielectronic oxidation process could be performed at peak A. The controlled potential oxidation of I was thus carried out at  $+0.9\text{V/SCE}$  on 2g scale in a non divided cell fitted with the cited electrode (a glassy carbon electrode as anode and a carbon rod as cathode). In our preliminary experiments, the current dropped rapidly from  $150\text{mA}$  to  $20\text{mA}$  and electrolysis took place over a 5-hour period (scheme 1). After the consumption of 2 Faradays per mol of substrate, the voltammogram showed the disappearance of the first oxidation peak at  $+0.9\text{V/SCE}$  (figure 2).

And the electrolysis was terminated when the current decreased by more than 95%. Water was added to the anolyte and methanol was carefully evaporated under reduced pressure. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ , and the organic phase was dried over  $\text{MgSO}_4$ . The solvents were evaporated under reduced pressure to afford a precipitated solid which was collected by filtration. The products were purified by column chromatography (compound II) (silica gel; chloroform for chloroform/ether). After purification, the product was characterized by  $^1\text{H NMR}$ , and  $^{13}\text{C NMR}$ .

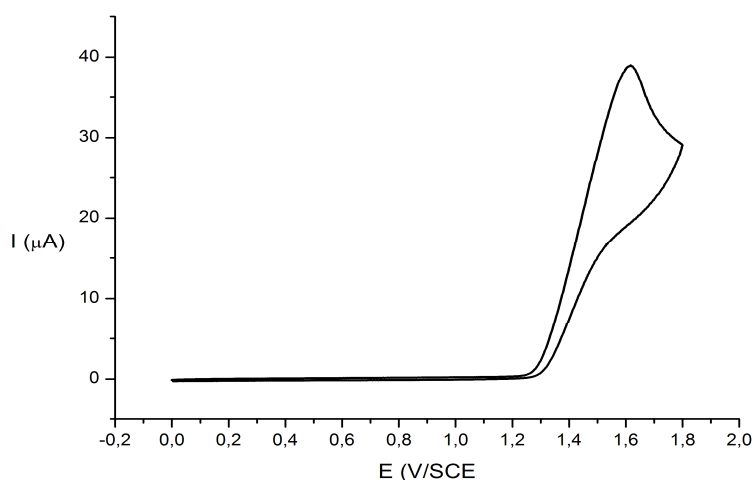


**Scheme 2.** electro synthesis of 5-(phenyl)-1,3,4-oxadiazol-2-amine II(a-h)

	<b>R</b>		<b>R</b>
<b>IIa</b>	4-Ome	<b>IIe</b>	4-NO <sub>2</sub>
<b>IIb</b>	H	<b>IIf</b>	2,6-Cl
<b>IIc</b>	4-Me	<b>IIg</b>	3-OMe, 4-OH
<b>IId</b>	4-Cl	<b>IIh</b>	3-ethoxybenzene, 4-OMe

### 3.2.4 Voltammetric Determination of the 5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine

Prior to macroscale electrolysis, an analytical study was carried. The voltammetric study of the 5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine has been realised in the same condition of the starting compound **I** -Figure 2- (vitreous carbon electrode in methanol containing LiClO<sub>4</sub> (0.1 M) as supporting electrolyte at a sweep rate of 50 mVs<sup>-1</sup> (figure 2) . Peak potential were expressed according to an SCE reference electrode) . The former voltammogram shows one oxidation peak at (1,35V) and showed the disappearance of the first oxidation peak at (0,95V), this means that the starting compound is finished, and this oxidation peak correspond of the former oxadiazole which is stable under this experimental condition.

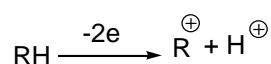


**Figure 2.** Cyclic voltammograms for 5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine

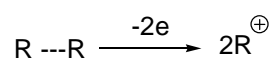
### 3.3. Discussion

Tow electron oxidation of the arylsemicarbazide (**I**) would be expected to generate the compound (**II**) capable of undergoing internal attack by either oxygen or nitrogen to yield the oxadiazole (**II**), deprotonation of the intermediary formed compound (**L**) could occur giving rise to the formation of the dipolar ion (**L1**) [30]. Contribution of structure of the dipolar formed compound should enhance cyclization through oxygen and formation of oxadiazole (**II**), under our condition oxadiazoles were the observed products (scheme 3). The patterns of the oxidative reaction of organic compound are classified into tow type's cleavage of C-H bond and C-C bond.

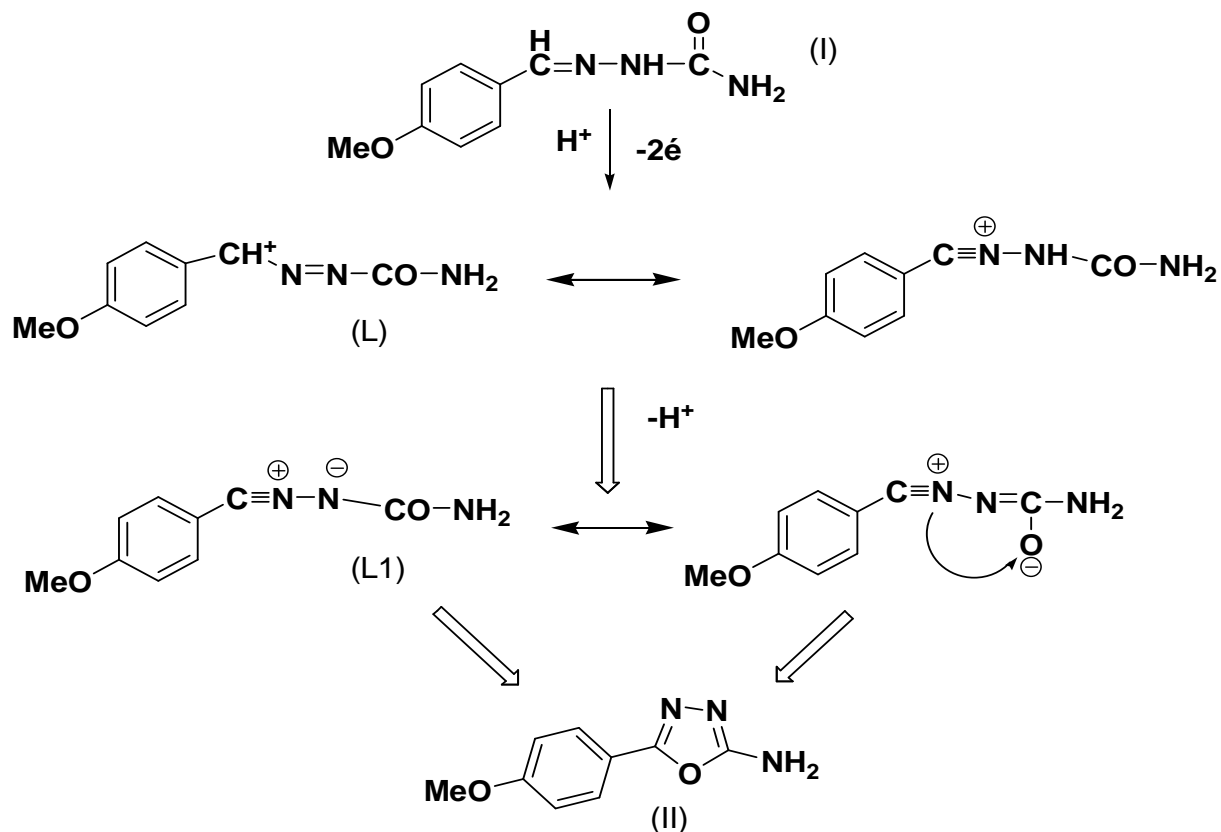
**C-H bond:**



**C-C bond:**



For our reaction, the proposed mechanism of the electro synthesis is:



**Scheme 3.** The proposed mechanism of the electro synthesis reaction

### 3.4. General Techniques

Melting points were determined in open capillary tubes and are uncorrected. Some products are known compounds and identified by comparison with authentic samples. Chemicals were purchased from Merck Chemical Company. H- and <sup>13</sup>C- NMR spectra were recorded on a Varian Gemini 200 spectrometer at 300 MHz in DMSO (internal standard TMS,  $\delta = 0.0$  ppm) at ambient temperature (ca 20 °C).

**Table 1.** Comparison of the electrochemical behaviours of the starting and obtained compounds

compound	I V/SCE		II V/SCE
	Peak A V	Peak B V	
b	0.95	1.45	1.5
c	1.00	1.51	1.55
d	0.95	1.50	1.54
e	0.88	1.40	1.44
f	0.90	1.35	1.40
g	0.97	1.30	1.45
h	0.99	1.42	1.50

Elemental analyses were measured in-house with a Carlo Erba 1106 EA instrument. TLC was performed on Kieselgel 60 F254 (Merck) layer Methanol: Dichloromethane (2:8 v/v) as eluents.

For the author compounds we I(b-c) we do the same work and analysis for the electrochemicals peak for each compounds (Table 1.).

### 3.5 The physical and analytical data of *Electrochemical* synthesized compounds

The structure of all the compounds are confirmed by.  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  spectre data and are further supported by correct elemental analysis.

*5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine IIa* The title compound was obtained in 52% overall yield mp: 245-249°C,  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  3,73(s,3H), 6,20(s,2H), 6,38 (d, J=8,5Hz, 2H), 7,37(d, J=8,5Hz, 2H)  $\text{C}^{13}\text{RMN}$  (DMSO- $d_6$ ) 55,9, 110,5, 114,8, 120,5, 128,5, 160,7, 164,5. Anal. Calcd for  $\text{C}_9\text{H}_9\text{N}_3\text{O}_2$ ; C, 56.54; H, 4.74; N, 21.98; O, 16.74. Found C, 56.50; H, 4.78; N, 21.95; O, 16.77

*5-phenyl-1,3,4-oxadiazol-2-amine IIb* The title compound was obtained in 60% overall yield mp 220-222°C,  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  7,1(s,2H), 7,22-7,30 (m, 2H), 7,33(d, J=7,5, 2H), 7,48(d, J=7,7, 2H),  $\text{C}^{13}\text{RMN}$  (DMSO- $d_6$ ) 65,5, 126,2, 128, 130,5, 132,5, 164,5. Anal. Calcd for  $\text{C}_8\text{H}_7\text{N}_3\text{O}$ ; C, 59.62; H, 4.38; N, 26.07; O, 9.93. found; C, 59.60; H, 4.40; N, 26.10; O, 9.90

*5-p-tolyl-1,3,4-oxadiazol-2-amine IIc* The title compound was obtained in 58% overall yield mp 210-218 °C,  $^1\text{H-NMR}$  DMSO : $\delta$  2,35 (s,3H), 6,43(s, 2H), 7,12(d, J=8,5Hz, 2H), 7,36(d, J=8,5Hz, 2H) .;  $\text{C}^{13}\text{RMN}$  (DMSO- $d_6$ )  $\delta$  24, 3, 123,2, 127,4, 129,6, 138,4 . Anal. Calcd for  $\text{C}_9\text{H}_9\text{N}_3\text{O}$ ; C, 61.70; H, 5.18; N, 23.99; O, 9.13. found C, 61.75; H, 5.13; N, 23.90; O, 9.23

*5-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine IIId* The title compound was obtained in 65% overall yield mp 231-234  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  7,12(s, 2H), 7.61(d, J=8,5Hz, 2H), 7.81(d, J=8,5Hz, 2H),  $\text{C}^{13}\text{RMN}$  (DMSO- $d_6$ )  $\delta$  123,4, 126,9, 129,5, 135, 156,7, 164,2 Anal. Calcd for:  $\text{C}_8\text{H}_6\text{ClN}_3\text{O}$ ; C, 49.12; H, 3.09; Cl, 18.12; N, 21.48; O, 8.18. Found C, 49.10; H, 3.11; Cl, 18.15; N, 21.47; O, 8.16

*5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine IIe* The title compound was obtained in 65% overall yield mp 255-257°C  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  7,52(s, 2H), 8,03(d, J=8,8Hz, 2H), 8,30(d, J=8,8Hz, 2H)  $\text{C}^{13}\text{RMN}$  (DMSO- $d_6$ )  $\delta$  124,8, 126,1, 130, 148,1, 156,2, 164,8 Anal. Calcd for;  $\text{C}_8\text{H}_6\text{N}_4\text{O}_3$ ; C, 46.61; H, 2.93; N, 27.18; O, 23.28. Found C, 46.57; H, 2.95; N, 27.20; O, 23.28

*5-(2,6-dichlorophenyl)-1,3,4-oxadiazol-2-amine IIIf* The title compound was obtained in 60% overall yield mp 210-212°C  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  7,1(s, 2H), 7,22-7,30 (m, 1H), 7,48(d, J= 7,7, 2H)  $\text{C}^{13}\text{RMN}$  (DMSO- $d_6$ )  $\delta$  60,5, 127,5, 131,6, 137,3, 137,7, 164,5 Anal. Calcd for;  $\text{C}_8\text{H}_5\text{Cl}_2\text{N}_3\text{O}$ ; C, 41.77; H, 2.19; Cl, 30.82; N, 18.27; O, 6.95. Found C, 41.79; H, 2.17; Cl, 30.80; N, 18.26; O, 6.98



*4-(5-amino-1,3,4-oxadiazol-2-yl)-2-methoxyphenol IIg* The title compound was obtained in 60% overall yield mp 210-212°C <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 3,73(s, 3H), 42(s, 2H), 681(d, J=75, 1H), 6,85(s, 1H), 6,9(d, J=77, 1H), 9,4(s, 1H), **C<sup>13</sup>RMN** (DMSO-d<sub>6</sub>) δ 56,2, 110,5 112,7, 117,4, 119,8, 121,2 145,4 154,2 164,2. Anal. Calcd for; C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>; C, 52.17; H, 4.38; N, 20.28; O, 23.17. Found C, 52.15; H, 4.39; N, 20.27; O, 23.19

*5-(4-methoxy-3-(phenoxymethyl)phenyl)-1,3,4-oxadiazol-2-amine IIIh* The title compound was obtained in 66% overall yield mp <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 5,33(s, 2H), 6,5(s, 2H), 6,72-6,87(m, 4H), 7,14-7,30 (m, 4H) **C<sup>13</sup>RMN** (DMSO-d<sub>6</sub>) δ 56.22, 61.3, 80.5, 114.5, 115.5, 118,7, 121.1, 127.4, 129,5, 129,8, 156.4, 160.4, 164.7 Anal. Calcd for; C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub> C, 64.64; H, 5.09; N, 14.13; O, 16.14. Found C, 64.60; H, 5.12; N, 14.10; O, 16.18.

#### 4. CONCLUSIONS

In conclusion, the anodic oxidation of the derivatives of arylsemicarbazides provides a convenient preparative route to the oxadiazoles and depending on the conditions selected for the reaction, so we developed a new method of the synthesis of oxadiazoles and other heterocyclic compounds can be also synthesized by the oxidative cyclization of carbonyl derivatives. In summary, 2,5-disubstituted-1,3,4-oxadiazoles, were synthesized from the arylsemicarbazides in a single step (one-pot electrolytic method) by utilizing electroorganic synthesis. Nevertheless, our results show that the direct electro oxidation process is higher, non polluting and safe than the chemical methods and it's easily controlled and gives good yield.

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