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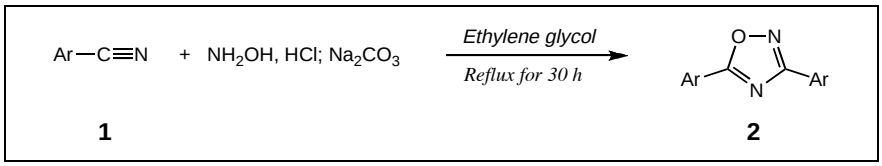

Disubstituted 1,2,4-oxadiazoles have been synthesized in good yields and good purity in one pot procedure by reaction of aromatic nitriles, hydroxylamine hydrochloride and sodium carbonate in ethylene glycol under heating at 195°C. The structures of different 1,2,4-oxadiazoles obtained were confirmed by ^{1}H, ^{13}C NMR and mass spectroscopy.

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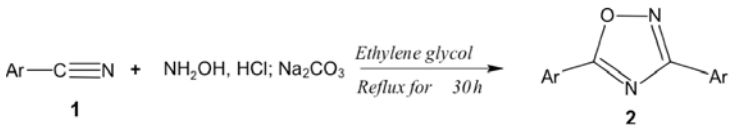
INTRODUCTION

Oxadiazoles are interesting heterocycles present in a variety of biological compounds such as coronary vasodilators, local anesthetics, anxiolytics [1] and diuretics [2]. These compounds can exhibit antimicotic properties [3], can act as anti-inflammatory agents [4] and were tested on their antibacterial activity against Staphylococcus Aureus, Streptococcus Pneumoniae, Escherichia Coli, Pseudomonas Aeruginosa, and Micrococcus [5,6]. Several methods are already described in the literature to synthesize 1,2,4-oxadiazoles [7], among them, the condensation of amidoximes with carboxylic acids in the presence of a coupling reagent [8] and the cycloaddition of nitrile oxides to amidoximes in solution and on solid support [9,10]. As a part of a program directed to obtain 3,5-disubstituted 1,2,4-oxadiazole molecules which can be used as corrosion inhibitors [11], we have finalized a simple new one step synthesis of the 3,5-disubstituted 1,2,4-oxadiazoles from aromatic nitriles and hydroxylamine hydrochloride. The 3,5-disubstited 1,2,4-oxadiazoles **2a-k** were obtained in excellent yields and good state of purity. It has been demonstrated that in the thiadiazole series, the unsymmetrical 1,2,4-thiadiazole was more efficient than the symmetrical one, the 1,3,4-thiadiazole, against acid corrosion of mild steel [12], and we hope to study this effect with some oxadiazoles compounds. The properties of these new compounds, as corrosion inhibitors, are under investigation (Scheme 1). The reaction between aromatic nitriles and hydroxylamine hydrochloride leads first to the formation of amidoximes. The latter and nitriles in ethylene glycol were converted into the final 3,5-diaryl 1,2,4-oxadiazoles. In ethylene glycol, the 3,5-disubstited 1,2,4-oxadiazoles **2a-k** were obtained in good yields and excellent state of purity.

RESULTS AND DISCUSSION

Compounds (**2a-k**) were prepared by condensation of aromatic nitriles with hydroxylamine hydrochloride in a mixture of sodium carbonate in ethylene glycol

Scheme 1



1, 2a	Ar = C_6H_5	**1, 2g**	Ar = 3,4-$CH_3OC_6H_3$
b	Ar = 2-pyridyl	**h**	Ar = 2,6-$CH_3OC_6H_3$
c	Ar = 3-pyridyl	**i**	Ar = 4-$CH_3C_6H_4$
d	Ar = 4-pyridyl	**j**	Ar = 4-ClC_6H_4
e	Ar = 3-$CH_3OC_6H_4$	**k**	Ar = 4-$NO_2C_6H_4$
f	Ar = 4-$CH_3OC_6H_4$		

(Scheme 1). The reaction between aromatic nitriles and hydroxylamine hydrochloride leads first to the formation of amidoximes. The latter and nitriles in ethylene glycol were converted into the final 3,5-diaryl 1,2,4-oxadiazoles. In ethylene glycol, the 3,5-disubstituted 1,2,4-oxadiazoles **2a-k** were obtained in good yields and excellent state of purity. The mechanism of the addition reaction of the aromatic nitriles **1a-k** with hydroxylamine hydrochloride to the corresponding amidoximes intermediate is given in Scheme 2. The oxime function can exist in two forms, the classical structure and the zwitterion structure [13]. These forms have been evidenced by X-ray diffraction studies [14,15].

In the case of amidoximes the hydrogen atom born by the nitrogen atom of the oxime function can migrate to the nitrogen atom of the amino group and this latter form can react easily with the nitrile group. The mechanism is presented in Scheme 2. The evolution of the reaction has been followed by measuring the release of ammonia during the formation of 1,2,4-oxadiazoles. This reaction takes place in good yields in ethylene glycol at 195°C for 30 hours (Table).

EXPERIMENTAL

Melting points were determined with on an IA 9000 series Electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker F.T. AC 300 spectrometer (300 MHz for ^{1}H nmr and 75 MHz for ^{13}C nmr) using dimethyl-d_6 sulfoxide (DMSO). Matrix assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOF-MS) are used to record the mass spectra of the oxadiazole compounds. All starting materials were of reagent grade and used as purchased.

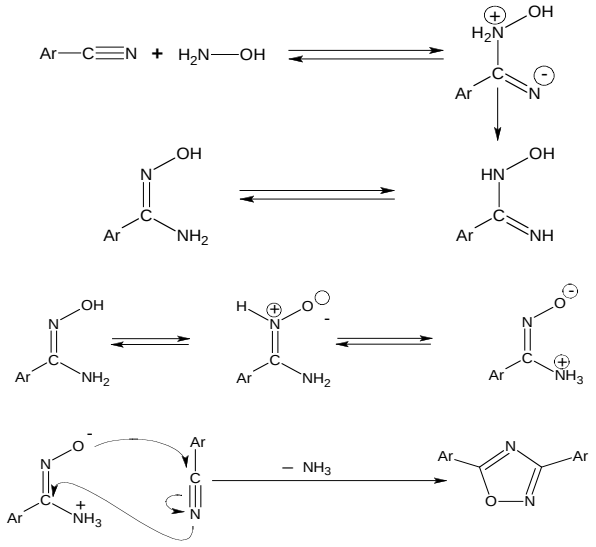
General Procedure for the Synthesis of Oxadiazole 2a-k. A solution of sodium carbonate (0.05 mol) in water (5 ml) was added to a mixture of aromatic nitriles **1a-k** (0.05 moles) and hydroxylamine hydrochloride (0.05 moles) in ethylene glycol (15 ml). The resulting mixture was heated under reflux (T= 195°C) for 30 hours with vigorous stirring. After cooling, the reaction mixture was filtered in order to remove the sodium chloride formed during the reaction and 100 ml water was added to dilute the solvent. Upon allowing the reaction mixture to cool, colourless crystals separated which were removed by filtration. The resulting solid was crystallized from ethanol and dried under vacuum. Yields, Mp and elemental analysis are given in Table. ^{1}H, ^{13}C nmr, MS and elemental analysis: data are in accordance with the proposed structures, are given below.

Table 1

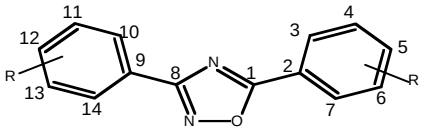
Physical and Analytical Data of 2,5-Diaryl-1,2,4-oxadiazoles **2a-k**.

Compound No.	Ar	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd./Found			Ref
					C	H	N	
2a	C_6H_5	75	110	$C_{14}H_{10}N_2O$	75.66 75.81	4.54 4.69	12.60 12.51	16
2b	2-pyridyl	57	174	$C_{12}H_8N_4O$	64.28 64.23	3.60 3.75	24.99 24.86	17
2c	3-pyridyl	66	170	$C_{12}H_8N_4O$	64.28 64.41	3.60 3.71	24.99 24.82	18
2d	4-pyridyl	80	183	$C_{12}H_8N_4O$	64.28 64.79	3.60 4.00	24.99 24.80	18
2e	3-$OCH_3C_6H_4$	82	96	$C_{16}H_{14}N_2O_3$	68.07 68.31	5.00 5.12	9.92 9.79	—
2f	4-$OCH_3C_6H_4$	91	127	$C_{16}H_{14}N_2O_3$	68.07 68.28	5.00 5.15	9.92 9.75	19
2g	3,4-$(OCH_3)_2C_6H_3$	71	178	$C_{18}H_{18}N_2O_5$	63.15 63.36	5.30 5.47	8.18 8.09	—
2h	2,6-$(OCH_3)_2C_6H_3$	62	126	$C_{18}H_{18}N_2O_5$	63.15 63.40	5.30 5.41	8.18 8.12	—
2i	4-$CH_3C_6H_4$	76	133-134	$C_{16}H_{14}N_2O$	76.78 76.95	5.64 5.78	11.19 11.09	20
2j	4-ClC_6H_4	88	183	$C_{14}H_8Cl_2N_2O$	57.76 57.45	2.77 2.98	9.62 9.48	21
2k	4-$NO_2C_6H_4$	70	235	$C_{14}H_8N_4O_5$	53.85 54.01	2.58 2.69	17.94 17.83	—

Scheme 2



The general formula of the parent oxadiazoles with corresponding numbering scheme is given below:



3,5-Bis(phenyl)-1,2,4-oxadiazole (**2a**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.67 (m, 6H); 8.09 (d, J = 7.63 Hz, 1H); 8.13 (d, J = 7.63 Hz, 1H); 8.17 (d, J = 6.41 Hz, 1H); 8.21(d, J = 6.41 Hz, 1H). ^{13}C nmr (DMSO-d_6): δ (ppm) 175.42 (C_1), 126.12 (C_2), 129.56 (C_3), 129.27 (C_4), 133.36 (C_5), 129.27 (C_6), 129.56 (C_7), 168.25 (C_8), 123.35 (C_9), 127.90 (C_{10}), 127.09 (C_{11}), 131.66 (C_{12}), 127.09 (C_{13}), 127.90 (C_{14}). MALDI-TOFMS: *m/z* 223 (M +1).

3,5-Bis(2-pyridyl)-1,2,4-oxadiazole (**2b**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.65 (t, J = 6.10 Hz, 1H); 7.75 (t, J = 6.71 Hz, 1H); 8.13 (m, 3H); 8.36 (d, J = 7.63 Hz, 1H); 8.84 (d, J = 6.72 Hz, 2H). ^{13}C nmr (DMSO-d_6): δ (ppm) 174.89 (C_1), 145.46 (C_2), 124.51 (C_3), 138.19 (C_4), 127.58 (C_5), 150.58 (C_6), 168.95 (C_8), 142.66 (C_9), 150.35 (C_{11}), 126.28 (C_{12}), 137.81 (C_{13}), 123.44 (C_{14}). MALDI-TOFMS: *m/z* 225 (M +1).

3,5-Bis(3-pyridyl)-1,2,4-oxadiazole (**2c**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.70 (m, 2H); 8.45 (t, J= 3.36 Hz, 1H); 8.56 (t, J= 7.93Hz, 1H); 8.82 (d, J= 3.36 Hz, 1H); 8.90 (d, J= 3.36 Hz, 1H); 9.26 (s,1H); 9.36(s,1H). ^{13}C nmr (DMSO-d_6): δ (ppm) 173.75 (C_1), 121.80 (C_2), 148.11 (C_3), 153.38 (C_5), 124.08 (C_6), 135.22 (C_7), 166.18 (C_8), 119.42 (C_9), 147.40 (C_{10}), 152.12 (C_{12}), 123.97 (C_{13}), 134.34 (C_{14}). MALDI-TOFMS: *m/z* 225 (M +1).

3,5-Bis(4-pyridyl)-1,2,4-oxadiazole (**2d**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.99 (d, J = 4.10 Hz, 2H); 8.07 (d, J = 4.22 Hz, 2H); 8.83 (d, J = 4.22 Hz, 2H); 8.90 (d, J = 4.10 Hz, 2H). ^{13}C nmr (DMSO-d_6): δ (ppm) 174.55 (C_1), 132.99 (C_2), 121.28 (C_3), 151.05 (C_4), 151.05 (C_6), 121.28 (C_7), 167.19 (C_8), 130.00 (C_9), 120.97 (C_{10}), 150.75 (C_{11}), 150.75 (C_{13}), 120.97 (C_{14}). MALDI-TOFMS: *m/z* 225 (M +1).

3,5-Bis(3-methoxyphenyl)-1,2,4-oxadiazole (**2e**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.18 (d, J = 6.11 Hz, 2H); 7.29 (d, J = 8.25 Hz, 2H) 7.51-7.74 (m, 4H) 3.86 (s, 6H) OCH_3. ^{13}C nmr (DMSO-d_6): δ (ppm) 175.24 (C_1), 127.29 (C_2), 130.84 (C_3), 130.51 (C_4), 117.50 (C_5), 168.12 (C_6), 119.39 (C_7), 159.66 (C_8), 124.41 (C_9), 120.20 (C_{10}), 120.20 (C_{11}), 112.43 (C_{12}), 159.60 (C_{13}), 111.93 (C_{14}), substituent 55.31 and 55.49. MALDI-TOFMS: *m/z* 283 (M +1).

3,5-Bis(4-methoxyphenyl)-1,2,4-oxadiazole (**2f**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.10 (d, J = 8.56 Hz, 2H); 7.17 (d, J = 8.86 Hz, 2H); 8.0 (d, J = 8.86 Hz, 2H); 7.11 (d, J = 8.56 Hz, 2H) 3.83 (s, 3H) OCH_3 3.86 (s,3H) OCH_3. ^{13}C nmr (DMSO-d_6): δ (ppm) 174.96 (C_1), 118.55 (C_2), 129.89 (C_3), 114.98 (C_4), 163.05 (C_5), 114.63 (C_6), 129.89 (C_7), 167.79 (C_8), 115.79 (C_9), 128.75 (C_{10}), 114.63 (C_{11}), 161.71 (C_{12}), 114.98 (C_{13}), 128.75 (C_{14}), substituent 55.39 and 55.64. MALDI-TOFMS: *m/z* 283 (M +1).

3,5-Bis(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (**2g**). ^{1}H nmr (DMSO-d_6): δ (ppm) 6.76 (d, J = 8.55Hz, 4H); 7.57 (s, 2H), 3.85 (s, 12H) OCH_3. ^{13}C nmr (DMSO-d_6): δ (ppm) 173.14 (C_1), 129.94 (C_2), 114.04 (C_3), 157.37 (C_4), 154.22 (C_5), 121.02 (C_6), 126.31 (C_7), 166.89 (C_8), 125.66 (C_9), 107.72 (C_{10}), 152.43 (C_{11}), 153.86 (C_{12}), 111.13 (C_{13}), 124.28 (C_{14}), substituent 55.46 and 56.81. MALDI-TOFMS: *m/z* 343 (M +1).

3,5-Bis(2,6-dimethoxyphenyl)-1,2,4-oxadiazole (**2h**). ^{1}H nmr (DMSO-d_6): δ (ppm) 6.75 (d, J = 8.53Hz, 4H); 7.55 (d, J = 8.55Hz, 2H), 3.85 (s, 12H) OCH_3. ^{13}C nmr (DMSO-d_6): δ (ppm) 177.52 (C_1), 106.71 (C_2), 160.25 (C_3), 111.65 (C_4), 133.47 (C_5), 111.65 (C_6), 160.25 (C_7), 170.38 (C_8), 104.06 (C_9), 152.23 (C_{10}), 109.11 (C_{11}), 130.12 (C_{12}), 109.11 (C_{13}), 152.23 (C_{14}), substituent 55.02 and 55.73. MALDI-TOFMS: *m/z* 343 (M +1).

3,5-Bis(4-methylphenyl)-1,2,4-oxadiazole (**2i**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.21-7.30 (m, 4H); 7.76 (d, J = 7.93 Hz, 2H); 7.87 (d, J = 7.93 Hz, 2H), 2.31 (s, 3H) CH_3, 2.35 (s, 3H) CH_3. ^{13}C nmr (DMSO-d_6): δ (ppm) 175.55 (C_1), 127.44 (C_2), 131.19 (C_3), 129.17 (C_4), 143.53 (C_5), 129.17 (C_6), 131.19 (C_7), 168.78 (C_8), 127.02 (C_9), 129.23 (C_{10}), 128.72 (C_{11}), 141.17 (C_{12}), 128.72 (C_{13}), 129.23 (C_{14}), substituent 20.85 and 21.07. MALDI-TOFMS: *m/z* 251 (M +1).

3,5-Bis(4-chlorophenyl)-1,2,4-oxadiazole (**2j**). ^{1}H nmr (DMSO-d_6): δ (ppm) 7.03 (d, J = 7.03 Hz, 2H); 7.11 (d, J = 7.95 Hz, 2H); 7.49 (d, J = 7.03 Hz, 2H); 7.87 (d, J = 7.33 Hz, 2H). ^{13}C nmr (DMSO-d_6): δ (ppm) 170.89 (C_1), 125.18 (C_2), 132.11 (C_3), 128.55 (C_4),139.40 (C_5),128.76 (C_6), 132.11 (C_7), 166.32 (C_8), 124.31 (C_9), 129.68 (C_{10}),127.12(C_{11}),136.15 (C_{12}), 127.12 (C_{13}), 129.68 (C_{14}). MALDI-TOFMS: *m/z* 292 (M +1).

3,5-Bis(4-nitrophenyl)-1,2,4-oxadiazole (**2k**). ^{1}H nmr (DMSO-d_6): δ (ppm) 8.08 (d, J = 8.56 Hz, 2H); 8.18-8.30 (m, 6H). ^{13}C nmr (DMSO-d_6):δ (ppm) 171.37 (C_1), 139.89 (C_2), 130.66 (C_3), 123.76 (C_4),150.16 (C_5), 130.66 (C_6), 128.86(C_7), 167.25 (C_8), 135.19 (C_9), 128.86 (C_{10}),123.40(C_{11}), 149.00 (C_{12}), 123.40 (C_{13}), 123.76 (C_{14}). MALDI-TOFMS: *m/z* 313 (M +1).

REFERENCES AND NOTES

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