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Novel, fast and efficient one-pot sonochemical synthesis of 2-aryl-1,3,4-oxadiazoles

Morteza Rouhani[1], Ali Ramazani[1,*] and Sang Woo Joo[2,*]

[1]*Department of Chemistry, University of Zanjan, P O Box 45195-313, Zanjan, Iran*

**E-mail: aliramazani@gmail.com*

[2]*School of Mechanical Engineering, Yeungnam University, Gyeongsan 712-749, Republic of Korea*

**E-mail: swjoo@yu.ac.kr*

Abstract

Ultrasound promoted synthesis of 2-aryl-1,3,4-oxadiazoles at ambient temperature is reported. The remarkable features of the new procedure are shorter reaction time, excellent yields, cleaner reaction profile and simple experimental and workup procedure.

Keywords:

Ultrasound, 1,3,4-oxadiazoles, *N*-isocyanoiminotriphenylphosphorane, intramolecular *aza*-Wittig reaction, isocyanide.

1.Introduction

During the past decade, isocyanide-based multicomponent reactions (IMCRs) gained significant interest within the scientific community as an efficient, convenient, time-saving, and atom-economical approach to a variety of drug-like small heterocyclic molecules [1]. 1,3,4-oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides. They are an important class of heterocyclic compounds that have a

wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, and antihypertensive [2-5]. Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles [2-6]. These protocols are multi-step in nature [7-12]. The most general method involves the cyclization of diacylhydrazides with a variety of reagents, such as thionyl chloride, phosphorusoxychloride or sulfuric acid, usually under harsh reaction conditions. Few reliable and operationally simple examples have been reported for the one-step synthesis of 1,3,4-oxadiazoles, especially from readily available carboxylic acids and acid hydrazides [13].

Iminophosphoranes are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products-compounds with biological and pharmacological activity [14]. Recently, we have explored the organic chemistry of *N*-isocyanoiminotriphenylphosphorane (2) [15-16]. *N*-isocyanoiminotriphenylphosphorane (2) has valuable synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality [17-18].

In the last few years, the application of ultrasound in synthetic organic chemistry became more and more interesting [19-25]. ‘‘Sonochemistry’’ is a new trend in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation in high yields, short reaction times and mild conditions [26-30]. Cavitation is the formation, growth and collapse of bubbles in an irradiated liquid. This effect induces very high local pressure and temperatures inside the bubbles and enhances mass transfer and turbulent flow in the liquid. Rayleigh’s early descriptions of a mathematical model for the collapse of cavities in incompressible liquids predicted enormous local temperatures and pressures [31]. Ultrasound has been utilized to accelerate a number of

synthetically useful reactions, especially in heterocyclic chemistry. The literature reports the sonochemistry synthesis of 1,2,4-oxadiazoles [32], benzoxazoles [33], pyrazoles [34], thiazoles [35], isoxazoles [36], imidazolines [37], thiazolidinones [38], triazoles [39], pyrimidines [40], pyrazolopyridines [41], thiazinanones [42]. Motivated by the afore-mentioned findings, and in a continuation of our interest in synthesis of a wide range of heterocyclic systems, for biological screening programme in our laboratory [43–46], and as a part of our growing interest in sonochemistry [47], we describe here a facile sonochemical synthesis of some novel 1,3,4-oxadiazoles (5) from benzoic acid derivatives (1) and *N*-isocyanoiminotriphenylphosphorane (2) in excellent yields under ultrasonic irradiation (Scheme 1).

Scheme 1

2. Experimental

2.1 General

All reagents were obtained from commercial sources and used without further purification. *N*-isocyanoiminotriphenylphosphorane (2) was prepared based on a reported procedure [48]. Reactions were monitored by TLC carried out on precoated glass-backed plates Merck 60 HF_{254} (0.25 mm) with UV light. Melting points were determined by Electrothermal 9100 apparatus and are uncorrected. IR spectra were taken on a Jasco 6300 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-250 Avance spectrometer at 250.0 and 62.5 MHz, respectively. MS were determined on Esquire Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 20 eV. Sonication was performed in a Bandelin SONOPULS ultrasonic homogenizers (made in Germany) with 20 kHz processing frequency, a nominal power 250 W, uniform sonic waves and constant sound radiation.

2.2 Classical procedure for the synthesis of 2-aryl-1,3,4-oxadiazoles.

The classical procedure was operated based on our previous work [16]. To a magnetically stirred solution of *N*-isocyanoiminotriphenylphosphorane (2) (0.302 g, 1 mmol) in dry CH_2Cl_2 (4 mL), a solution of 2-aryl-benzoic acid derivatives (1) (1 mmol) in dry CH_2Cl_2 (4 mL) was added. The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the viscous residue was purified by precoated glass-backed plates [silica gel; petroleum ether/ethyl acetate (10:2)]. The solvent was removed under reduced pressure, and the product (5) was obtained.

2.3 Ultrasound-promoted synthesis of 2-aryl-1,3,4-oxadiazoles.

To a solution of *N*-isocyanoiminotriphenylphosphorane (2) (0.302 g, 1 mmol) in dry CH_2Cl_2 (4 mL), a solution of 2-aryl-benzoic acid derivatives (1) (1 mmol) in dry CH_2Cl_2 (4 mL) was added and the mixture was sonicated in an ultrasonic cleaner at room temperature. The solvent was removed under reduced pressure, and the viscous residue was purified by precoated glass-backed plates [silica gel; petroleum ether/ethyl acetate (10:2)]. The solvent was removed under reduced pressure, and the product (5) was obtained.

2.4 Data spectra of products

2.4.1 Compound 5a

2-phenyl-1,3,4-oxadiazole. White crystal; m.p:143.6°C; Yield: 97%. IR(KBr) (ν_{max},cm^{-1}): 3007.69, 1692.31, 1661.54, 1530.77, 723.08. ^{1}H NMR ($CDCl_3$) δ_H: 8.42(s, 1H, oxadiazole); 8.10-8.06(m, 2H, arom); 7.59-7.48(m, 3H, arom). ^{13}C NMR ($CDCl_3$) δ_C: 164.79(1C, oxadiazole);

152.67(1CH, oxadiazole) ; 132.03, 129.127 and 127.10(5Ch, arom), 123.42(1C, arom). Chemical Formula: $C_8H_6N_2O$. MS *m/z* (%): 51(27) 77(80), 105(100),146(2).

2.4.2 Compound 5b

2-m-tolyl-1,3,4-oxadiazole. White crystal; m.p:64.4°C; Yield: 96%. IR(KBr) (ν_{max},cm^{-1}): 3107.69, 2984.62, 2407.69, 2276.92, 1553.85, 1500.12, 1115.38, 730.77. ^{1}H NMR ($CDCl_3$) δ_H: 8.46(s, 1H, oxadiazole); 7.96-7.83(m, 1H, arom); 7.43-7.34(m, 3H, arom); 2.429(s, 3H,CH_3). ^{13}C NMR ($CDCl_3$) δ_C: 164.90(1C, oxadiazole); 152.56(1CH, oxadiazole); 132.80, 129.01, 127.61, 124.21(4CH, arom); 139.02, 123.33(2C, arom); 21.32(1C, CH_3). Chemical Formula: $C_9H_8N_2O$. MS *m/z* (%): 41(40), 43(83), 51(74), 65(52), 77(84), 91(55), 104(35), 119(92), 160(100).

2.4.3 Compound 5c

2-p-tolyl-1,3,4-oxadiazole. White crystal; m.p:86.9°C; Yield: 97%. IR(KBr) (ν_{max},cm^{-1}): 3123.08, 2915.38, 1615.38, 1500.06, 1100.10, 953.85, 830.77, 738.46. ^{1}H NMR ($CDCl_3$) δ_H: 8.44(s, 1H, oxadiazole), 7.97(d, 2H, $^3J_{HH}$=8.25 Hz, arom), 7.32(d, 2H, $^3J_{HH}$=8.00Hz, arom), 2.43(s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ_C: 164.89(1C, oxadiazole); 152.37(1CH, oxadiazole); 142,58 and 120.70(2C, arom), 129.81 and 127.03(4CH, arom), 21.65(1C, CH_3). Chemical Formula: $C_9H_8N_2O$. MS *m/z* (%): 41(17), 51(24), 57(26), 77(35), 91(31), 104(22), 119(79), 149(67), 160(100).

2.4.4 Compound 5d

2-(3-chlorophenyl)-1,3,4-oxadiazole. White crystal; m.p:115.3°C; Yield: 91%. IR(KBr) (ν_{max},cm^{-1}): 3030.77, 2923.08, 1553.85, 1123.08, 776.92. ^{1}H NMR ($CDCl_3$) δ_H: 8.50(s, 1H, oxadiazole); 8.08(d, 1H, $^4J_{HH}$=1.5Hz, arom); 8.02-7.97(m, 1H, arom); 7.57-7.53(m, 1H, arom); 7.50-7.45(m, 1H, arom). ^{13}C NMR ($CDCl_3$) δ_C: 163.17(1C, oxadiazole), 152.84(1CH, oxadiazole), 135.28 and

125.07(2C, arom), 132.09, 130.52, 127.11 and 125.20(4CH, arom). Chemical Formula: $C_8H_5ClN_2O$. MS *m/z* (%): 51(29), 65(25), 77(85), 105(100), 149(58), 181(31).

2.4.5 Compound 5e

2-(4-chlorophenyl)-1,3,4-oxadiazole. White crystal; m.p: 127.1-128.4°C; Yield: 92%. IR(KBr) (ν_{max},cm^{-1}): 3076.92, 1607.69, 1484.62, 1092.31, 838.46, 738.40. ^{1}H NMR ($CDCl_3$) δ_H: 8.49(s, 1H, oxadiazole); 8.03(d, 2H, $^3J_{HH}$=8.5Hz, arom); 7.50(d, 2H, $^3J_{HH}$=8.25Hz, arom). ^{13}C NMR ($CDCl_3$) δ_C: 164.01(1C, oxadiazole), 152.73(1CH, oxadiazole), 138.36 and 121.92(2C, arom); 129.55 and 128.38 (4CH, arom). Chemical Formula: $C_8H_5ClN_2O$ MS *m/z* (%): 41(57), 43(89), 57(76), 71(39), 89(20), 111(15), 113(16), 139(34), 49(100), 167(36), 180(32).

2.4.6 Compound 5f

2-(4-fluorophenyl)-1,3,4-oxadiazole. White crystal; m.p:142.1°C; Yield: 91%. IR(KBr) (ν_{max},cm^{-1}): 3071.86, 2931.56, 1615.38, 1500.02, 1238.46, 846.15, 746.15. ^{1}H NMR ($CDCl_3$) δ_H: 8.47(s, 1H, oxadiazole); 8.13-8.06(m, 2H, arom); 7.26-7.18(m, 2H, arom). ^{13}C NMR ($CDCl_3$) δ_C: 166.94(1C, oxadiazole); 163.43(d, 1C, $^1J_{CF}$=66.87Hz, arom); 152.61(1CH, oxadiazole), 129.41(d, 2CH, $^3J_{CF}$=8.75Hz, arom) 119.78(s,1C, arom), 116.5(d, 2CH, $^2J_{CF}$=22.5Hz arom). Chemical Formula: $C_8H_5FN_2O$. MS *m/z* (%): 43(86), 57(31), 77(94), 105(100), 149(56), 164(10).

2.4.7 Compound 5g

2-(4-bromophenyl)-1,3,4-oxadiazole. White crystal; m.p: 140.2°C; Yield: 96%. IR(KBr) (ν_{max},cm^{-1}): 3146.15, 3092.31, 2930.77, 1600.01, 1476.92, 1107.69, 830.77. ^{1}H NMR ($CDCl_3$) δ_H: 8.47(s, 1H, oxadiazole); 7.96(d, 2H, $^3J_{HH}$=8.75Hz,arom); 7.67(d, 2H, $^3J_{HH}$=8.75, arom). ^{13}C NMR ($CDCl_3$) δ_C: 164.11(1C, oxadiazole) ; 152.74(1CH, oxadiazole), 126.82 and 122.35(2C,

arom), 131.83 and 128.51(4CH, arom). Chemical Formula: $C_8H_5BrN_2O$. MS *m/z* (%): 41(53), 50(71), 62(58), 75(56), 89(100), 119(39), 183(54), 224(67).

2.4.8 Compound 5h

2-(4-Iodophenyl)-1,3,4-oxadiazole. White crystal; m.p: 149.5°C; Yield: 96%. IR(KBr) (ν_{max},cm^{-1}): 3461.54, 1684.62, 1592.31, 1323.08, 761.52. ^{1}H NMR ($CDCl_3$) δ_H: 8.47 (s, 1H, oxadiazole); 7.88 (d, 2H, $^3J_{HH}$=8.5 Hz, arom); 7.79(d, 2H, $^3J_{HH}$=7.00Hz, arom). ^{13}C NMR ($CDCl_3$) δ_C: 164.23 (1C, oxadiazole); 152.77 (1CH, oxadiazole); 138.43 and 128.41 (4CH, arom); 122.87 and 99.04 (2C, arom). Chemical Formula: $C_8H_5IN_2O$. MS *m/z* (%): 50(37), 63(26), 76(36), 89(32), 105(22), 149(14), 203(13), 231(56), 272(100).

2.4.9 Compound 5i

2-(3,5-Dimethoxy-phenyl)-[1,3,4]oxadiazole. White crystals; m.p: 113.3-114.1 °C; Yield: 86%. IR(KBr) (ν_{max},cm^{-1}): 3146.15, 3115.38, 2969.23, 2938.46, 1607.69, 1561.54, 1469.23, 1361.54, 1215.38, 1161.54, 1046.15, 838.46. ^{1}H NMR ($CDCl_3$) δ_H: 8.48 (s, 1H, oxadiazole), 7.21 (s, 2H, arom); 6.63(s, 1H, arom); 3.86 (2s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ_C: 164.70(1C, oxadiazole); 161.17(1CH, oxadiazole); 152.65 (2CH, arom), 124.89(1C, arom); 104.81 and 104.49(3CH, arom); 55.60 (2CH, OCH_3). Chemical Formula: $C_{10}H_{10}N_2O_3$. MS *m/z* (%): 41(45), 43(100), 57(44), 75(40), 91(10), 105(12), 122(11), 149(53), 167(18), 206(23).

2.4.10 Compound 5j

2-Naphthalen-2-yl-[1,3,4]oxadiazole. White crystals; m.p: 149.8-150.0°C ; Yield: 83%. IR(KBr) (ν_{max},cm^{-1}): 3007.69, 1661.54, 1530.77, 1269.23, 1207.69, 1030.77. ^{1}H NMR (DMSO-d_6) δ_H: 8.48 (s, 1H, oxadiazole); 8.15(d, 1H, $^4J_{HH}$= 2Hz, arom); 8.04-7.90(m, 4H, arom); 7.62-7.59(m, 2H, arom). ^{13}C NMR (DMSO-d_6) δ_C: 167.83(1C, oxadiazole); 160.44(1CH, oxadiazole); 134.82,

130.00, 128.42(3C, arom); 132.47, 129,39, 128.58, 128.51, 128.11, 127.37, 124.44(7CH, arom). Chemical Formula: $C_{12}H_8N_2O$. MS *m/z* (%): 41(4), 51(30), 69(10), 127(81), 155(100), 186(5), 196(34).

2.4.11 Compound 5k

2-Styryl-[1,3,4]oxadiazole. Vicose oil; Yield: 72%. IR(KBr) (ν_{max},cm^{-1}): 307.69, 1638.46, 1523.08, 1100.32, 976.92. ^{1}H NMR ($CDCl_3$) δ_H: 8.38 (s, 1H, oxadiazole); 7.58-7.55 (m, 2H, arom); 7.45-7.41(m, 3H, arom); 7.09(d, 1H, $^3J_{HH}$=16.5Hz, vinylic); 7.62 (d, 1H, $^3J_{HH}$=16.5 Hz, vinylic). ^{13}C NMR ($CDCl_3$) δ_C: 164.28(1C, oxadiazole); 152.00(1CH, oxadiazole), 139.85(1CH, vinylic); 134.53(1C, arom); 130.14, 129.03, 127.57(5CH, arom); 109.53(1CH, vinylic). Chemical Formula: $C_{10}H_8N_2O$. MS *m/z* (%): 51(7), 63(7), 77(8), 89(10), 103(7), 115(22), 171(100) 172(37).

2.4.12 Compound 5l

2-(1,3,4-oxadiazol-2-yl)aniline. Yellow crystal; m.p:145.3 $^{\circ}$C; Yield: 96%. IR(KBr) (ν_{max},cm^{-1}): 3430.77and 3338.46(NH_2), 3038.46, 2938.46, 2930.77, 2930.77, 2561.54, 1623.08, 1269.23, 1107.69, 753.85. ^{1}H NMR ($CDCl_3$) δ_H: 8.41(s, 1H, oxadiazole); 7.78-7.75(m, 1H, arom), 7.32-7.25(m,1H, arom); 6.79(t, 1H, $^3J_{HH}$=7.5Hz, arom); 6.73(s, 1H, arom), 5.69(2H, NH_2). ^{13}C NMR ($CDCl_3$) δ_C: 164.62(1C, oxadiazole); 150.91(1CH, oxadiazole); 147.01 and 105.38(2C, arom); 132.79, 127.99, 116,91 and 116.28(4CH, arom). Chemical Formula: $C_8H_7N_3O$. MS *m/z* (%): 41(21), 51(32), 65(28), 77(35), 92(26), 105(21), 120(51), 161(100).

2.4.13 Compound 5m

2-Biphenyl-4-yl-[1,3,4]oxadiazole. White crystals; m.p: 154.7-155.1°C; Yield: 91%. IR(KBr) (ν_{max},cm^{-1}): 3107.69, 3007.69, 1638.46, 1484.62, 1415.38, 1115.38, 1107.69, 738.46. ^{1}H NMR

($CDCl_3$) δ_H: 8.49 (s, 1H, oxadiazole); 8.15(d, $^3J_{HH}$=8.5Hz, 2H, arom); 7.75 (d, $^3J_{HH}$=8.75Hz, 2H, arom); 7.66-7.62(m, 2H, arom); 7.52-7.40(m, 3H, arom). ^{13}C NMR ($CDCl_3$) δ_C: 164.43(1C, oxadiazole); 152.61(1CH, oxadiazole); 144.74, 139.668, 122.22(3C, arom); 129.00, 128.25, 127.74; 127.56, 127.15(9CH, arom). Chemical Formula:$C_{14}H_{10}N_2O$. MS *m/z* (%): 41(5), 43(8), 57(10), 115(8), 152(31), 181(100), 221(12).

2.4.14 Compound 5n

2-Biphenyl-2-yl-[1,3,4]oxadiazole Viscose oil; Yield: 93%. IR(KBr) (ν_{max},cm^{-1}): 3030.77; 1640.23; 1469.23; 1284.62; 1123.08. 8.21 (s, 1H, oxadiazole); 8.00-7.93 (m, 1H, arom); 7.65-7.59(m, 1H, arom); 7.55-7.50 (m, 1H, arom); 7.49-7.43 (m, 2H, arom); 7.37-7.34 (m,2H, arom), 7.27-7.21 (m, 2H, arom). ^{13}C NMR ($CDCl_3$) δ_C: 165.39 (1C, oxadiazole); 152.85 (1CH, oxadiazole); 142.21, 140.14, 122.48 (3C, arom); 131.61, 131.03, 130.67, 128.60, 128.33, 127.70, 127.66(9CH, arom). Chemical Formula: $C_{14}H_{10}N_2O$. MS *m/z* (%): 41(3), 43(4), 57(3), 77(5), 115(2), 152(41), 181(100), 221(10).

3. Results and discussion

To achieve suitable conditions for the synthesis of 2-aryl-1,3,4-oxadiazoles (5), various reaction conditions have been investigated in the reaction of benzoic acid (1a) and *N*-isocyanoiminotriphenylphosphorane (2) as a model reaction.

3.1. Effect of solvent on the product yield

We examined the effects of the solvent through some experiments. To search for the optimal solvent, the ultrasonic-assisted reaction of benzoic acid (1a) and *N*-isocyanoiminotriphenylphosphorane (2) was examined using acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), ethanol (C_2H_5OH) and methanol (CH_3OH) as solvent respectively. The results were summarized in Table 1. As can be seen in Table 1, the reaction between benzoic acid (1a) with *N*-isocyanoiminotriphenylphosphorane (2) under ultrasonic irradiation at room temprature was solvent dependent. The reaction could be efficiently carried out in solvents such as dichloromethane and chloroform (Table 1, entries 2 and 3). The reaction using dichloromethane as the solvent resulted in higher yields and shorter reaction time than those using C_2H_5OH, CH_3OH and CH_3CN as solvents (product was obtained in 97% yield in 10 min). So, dichloromethane was chosen as the solvent for all further reactions.

Table 1

3.2. Influence of ultrasound power on product yield

As shown in Table 2, the product yield was affected by ultrasonic power. The highest product yield of 97% was obtained when ultrasonic power was 200 W. The reaction time and yield of 1a did not change from 200 to 250 W, therefore, 200W of ultrasonic irradiation was sufficient to push the reaction forward. The best yield for (1a) was obtained by ultrasonic irradiation for 10 min at room temperature and 200 W. Decreased yields were observed outside the optimum ultrasonic power. The reaction could not carry out completely because it had no enough energy when ultrasonic power was lower than 200 W. Without ultrasonic irradiation, the reaction needed at least 12 h with stirring and gained lower yield (91%).

Table 2

3.3. High efficiency and generality of synthesis by ultrasound irradiation

After detecting more efficient solvent (CH_2Cl_2), and power (200 W) to delineate the role of ultrasound, this method was examined by the reaction of several substituted benzoic acids, and *N*-isocyanoiminotriphenylphosphorane with and without ultrasonic irradiation at the same temperature in CH_2Cl_2 as solvent (Table 3-Figure).

Table 3

Figure

Table 4

When the reaction was carried out under conventional method it gave comparatively low yields of products and took longer reaction time, while the same reaction carried in the influence of ultrasonic irradiation gave excellent yields of product in short reaction time (Table 4). As is known, the influence of ultrasound on the reaction is that it can markedly shorten the reaction time compared with conventional conditions. The similar effect was also observed in our experiments. It is apparent that ultrasound irradiation can accelerate the reaction significantly to give better yield. The results in Table 4 show that ultrasound is much more efficient than magnetic stirring. Thus, ultrasonic irradiation was found to have beneficial effect on the

synthesis of 2-aryl-1,3,4-oxadiazoles derivatives. To the best of our knowledge, this new procedure provides the first example of an efficient and ultrasound-promoted one-pot three-component approach for the synthesis of disubstituted 1,3,4-oxadiazole derivatives.

3.4. The study of acceleration mechanism under irradiation of ultrasound

The benzoic acid derivative (1) and *N*-isocyanoiminotriphenylphosphorane (2) in dichloromethane (CH_2Cl_2) as solvent under ultrasonic irradiation at room temperature afforded one product and triphenylphosphine oxide (6) as byproduct in each case (as evidenced by TLC) (Scheme 1). The reaction proceeds very fast and cleanly under ultrasonic irradiation and no side reactions were observed. The mechanism of the reaction between the benzoic acid derivative (1) and *N*-isocyanoiminotriphenylphosphorane (2) has not been established experimentally. However, a possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of isocyanides [46], it is reasonable to assume that the protonation of (2) by carboxylic acid (1) followed by quenching of the cationic center by the conjugate base of the carboxylic acid can generate iminophosphorane (4) [14]. Intramolecular aza-Wittig [14] reaction of iminophosphorane (4) would lead to the formation of 2-aryl-1,3,4- oxadiazoles (5) and triphenylphosphine oxide (6) (Scheme 2, Table 3).

Scheme 2

Cavitation is the origin of sonochemistry. As ultrasound passes through a liquid, the liquid can produce bubbles. These bubbles can undergo a violent collapse, which generates very high pressures and temperatures, inducing molecular fragmentation, and highly reactive species are

locally produced. The implosion of cavities reportedly established an unusual environment for reactions. The gases and vapors inside the cavity are compressed, generating intense heat that raises the temperature of the liquid immediately surrounding the cavity and the high temperature and pressure produced during cavitation break their chemical bonds, short-lived chemical species are returned to the bulk liquid at room temperature, thus reacting with other species [49]. With this case in mind, we turned our attention to the reaction mechanism and the role of ultrasound irradiation played in the reaction. We believed that there were two main reasons for the acceleration in present system. One was the physical aspect of ultrasound which leaded *N*-isocyanoiminotriphenylphosphorane to dissolve faster in dichloromethane; another was the chemical aspect of ultrasound which accelerated the reaction. As is known in our previous work [16], in these type of reactions, deprotonation of the acid and the formation of O-centered nucleophiles occurred very slowly in the absence of ultrasound conditions. The ultrasonic irradiation played an important role in the formation of O-centered nucleophile while this may be the rate-determining step in the reaction. It has been observed that the yield of 5a in the absence of ultrasound irradiation was only 12% after 10 minutes. After 3h, 6h, 9h and 12h the yields was obtained 41%, 65%, 80% and 91% respectively. The yield of the reaction does not efficiently vary after 12h [16]. Based on the present work and the our previous work [16], the 12h is the shortest reaction time for this reaction to provide the yields of silent conditions. In the presence of ultrasound irradiation, localized ‘‘hot spots’’ generated from a violent collapse of the bubbles creates a transient high temperature and pressures, inducing molecular fragmentation, and highly reactive species are locally produced. In the presence of ultrasound irradiation, producing of the conjugate base of acid 1 goes more faster. Furthermore we believed that ultrasound waves disturbances the CH_2Cl_2 layer around benzoic acid derivative and *N*-

isocyanoiminotriphenylphosphorane and thus accelerates deprotonation speed in rate determining step. From the Table 4, it is indicated that the obvious difference in the reaction efficiencies with or without sonication suggests again that the reaction under ultrasound condition proceeded in not the same, but in more efficient way than did the reaction under the heating conditions. For example the yield of the related reaction to synthesize 5a is up to 97% under ultrasound condition at the room temperature, whereas the yield of the reaction without sonication is 91%, and the reaction time under sonication is reduced from 12 h to 10 min. Thus, ultrasound was found to have beneficial effect on the synthesis of 2-aryl-1,3,4-oxadiazoles 5a–n (Figure) in which decrease time of above reactions from 12 h in conventional procedure to less than 20 min, also, a noticeable improvement in yields of reactions under ultrasonic irradiations (Figure-Table 3).

In Summary, under ultrasound irradiation; the reaction is simple to execute and the products are isolated in good yields. The work-up is very simple. The reaction time is short (less than 20 min) and the products are obtained in excellent purity.

To the best of our knowledge, this new procedure provides the first example of an efficient and two-component method for the synthesis of 2-aryl-1,3,4-oxadiazoles under ultrasound irradiation. This method, based on two-component free-catalyst reaction under ultrasonic irradiation, is the most simple and convenient and would be applicable for the synthesis of different types of oxadiazoles.

4. Conclusion

In this work, we have developed a mild, highly efficient and improved protocol for the preparation of a series of 2-aryl-1,3,4-oxadiazoles. Our sonochemical method offers several

advantages over existing methods, including improved yields, cleaner reactions, simple work-up and very short reaction times, which makes it a useful and environmentally attractive strategy for the synthesis of oxadiazole derivatives.

Acknowledgements

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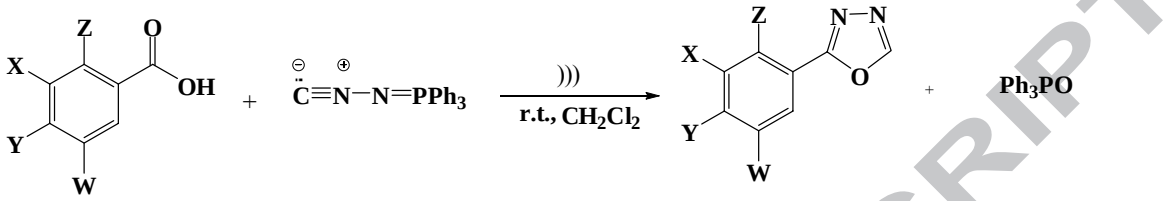
Scheme 1: One-pot two-component synthesis of 2-aryl-1,3,4-oxadiazoles under ultrasound irradiation.



Scheme 2: Proposed mechanism for the formation of 2-phenyl-1,3,4-oxadiazole derivatives **5a-n**.

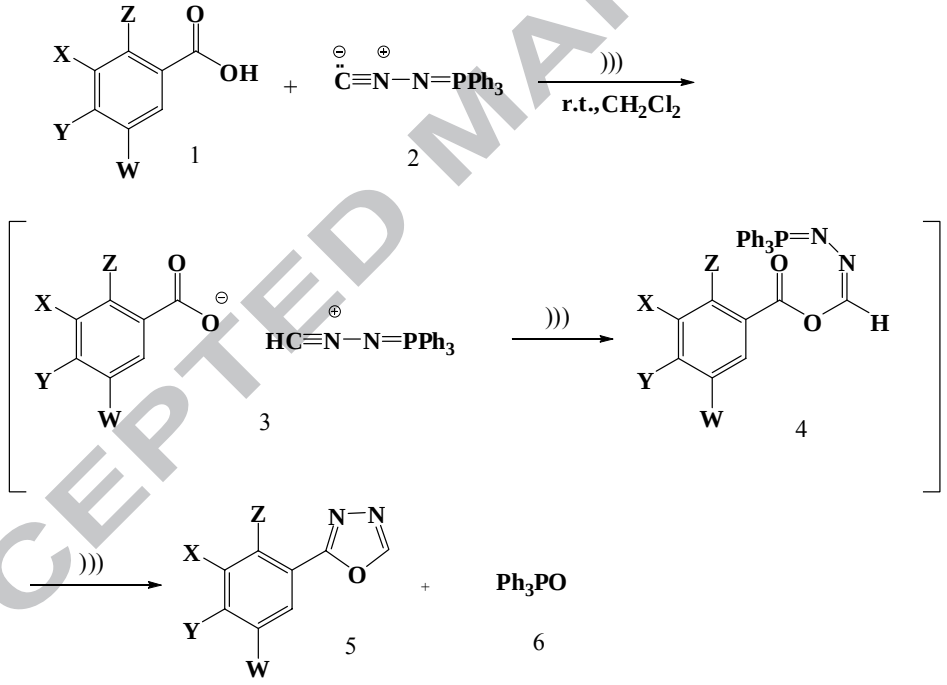
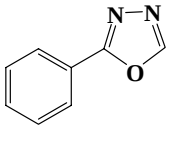
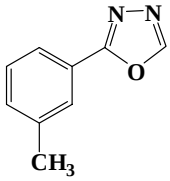


Figure: Two-component synthesis of 2-aryl-1,3,4-oxadiazoles derivatives 5a-n (See Table and Text).



5a



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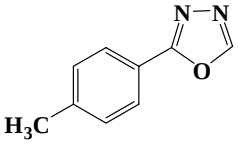

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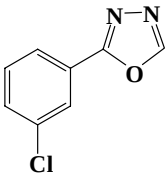

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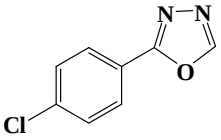

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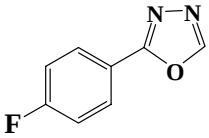

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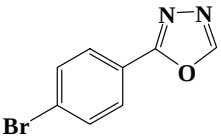

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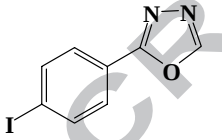

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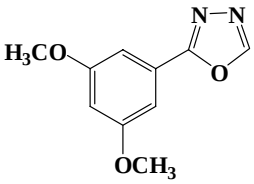

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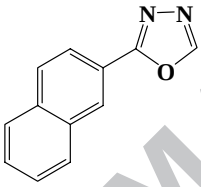

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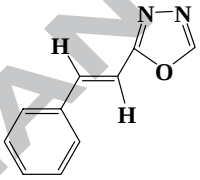

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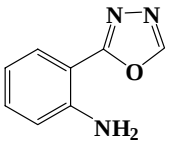

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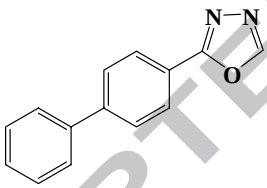

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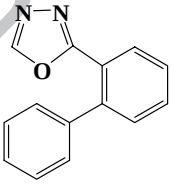


5n

Table 1: Synthesis of 2-phenyl-1,3,4-oxadiazole (5a) in different solvent systems under ultrasonic irradiation at room temperature.

Entry	Solvent	Time (min)	Yield[a](%)
1	Acetonitrile	13	63
2	CH_2Cl_2	10	97
3	$CHCl_3$	12	91
4	Ethanol	18	78
5	Methanol	21	71
6	Solvent free	30	21

[a] Isolated yield.

Table 2: Effect of the ultrasonic power in the synthesis of 2-phenyl-1,3,4-oxadiazole (5a)

Entry	Power (W)	Time (min)	Yield[a](%)
1	100	35	41
2	150	20	54
3	200	10	97
4	250	10	97

[a] Isolated yield.

Table 3: Synthesis of 1,3,4-oxadiazole derivatives 5.

Compound	Z	X	Y	W
5a	H	H	H	H
5b	H	$-CH_3$	H	H
5c	H	H	$-CH_3$	H

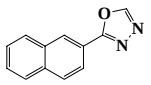
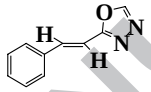
5d	H	Cl	H	H
5e	H	H	Cl	H
5f	H	H	F	H
5g	H	H	Br	H
5h	H	H	I	H
5i	H	$-OCH_3$	H	$-OCH_3$
5j				
5k				
5l	$-NH_2$	H	H	H
5m	H	H	-Ph	H
5n	-Ph	H	H	H

Table 4: Comparison of the times and yields of the reactions with or without sonication for the synthesis of 1,3,4-oxadiazole derivatives.

Compound	**With sonication[a]**		**Without sonication[b]**	
	Yield[c] (%)	**Time (min)**	**Yield[c] (%)**	**Time (min)**
5a	97	10	91	720
5b	96	13	91	720
5c	97	15	92	720
5d	91	15	85	720
5e	92	15	82	720
5f	91	14	84	720
5g	96	10	92	720
5h	96	11	91	720
5i	86	16	72	720

5j	83	16	72	720
5k	72	16	32	720
5l	96	14	85	720
5m	91	15	80	720
5n	93	15	80	720

[a] *Reaction condition:* Reaction of benzoic acid derivatives and *N*-isocyanoiminotriphenylphosphorane in CH_2Cl_2 under ultrasound irradiation.
[b] *Reaction condition:* Reaction of benzoic acid derivatives and *N*-isocyanoiminotriphenylphosphorane in CH_2Cl_2 at room temprature under high stirring condition.
[c] Yields of isolated products.