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Ultrasonics in isocyanide-based multicomponent reactions: A new, efficient and fast method for the synthesis of fully substituted 1,3,4-oxadiazole derivatives under ultrasound irradiation

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Abstract

A fast and convenient approach to the synthesis of fully substituted 1,3,4-oxadiazoles via three-component reaction of aromatic carboxylic acids, acenaphthoquinone, and (*N*-isocyanimino)triphenylphosphorane under ultrasound irradiation is described. Furthermore, a series of compounds were synthesized and characterized by melting point, IR, NMR and MS. Utilization of easy reaction conditions, very high to excellent yields, and short reaction times makes this manipulation potentially very useful.

Keywords

Ultrasound, 1,3,4-oxadiazoles, (*N*-isocyanimino)triphenylphosphorane, aromatic carboxylic acids, acenaphthoquinone, intramolecular *aza*-Wittig reaction, isocyanide.

1.Introduction

Multicomponent reactions (MCRs) [1-2] are referred to as the one-pot processes, where multiple bonds are formed among starting materials to furnish the product with essentially all of the atoms

of the reactants. Among the known multicomponent reactions, isocyanide based MCRs (IMCRs) are particularly valuable [3-4]. In addition to the added diversity of bond formation and functional group tolerance, the outstanding position of IMCRs can also be traced back to the exceptional reactivity of isocyanide. As we know, no other functional group reacts with nucleophiles and electrophiles at the same atom [5]. Consequently, MCRs involving isocyanides have been widely applied to organic synthesis, especially in drug discovery [6]. The *aza*-Wittig-type reaction has attracted much attention recently because of its high potential for the synthesis of a wide variety of nitrogen heterocycles, which can be attributed in the preparation of functionalized iminophosphoranes [7]. Through *aza*-Wittig reaction, iminophosphoranes with isocyanates, carbon dioxide, or carbon disulfide can easily be converted into functionalized hetero-cumulenes [7]. The nucleophilicity at the nitrogen is an important factor in the use of these iminophosphoranes as *aza*-Wittig reagents. Iminophosphoranes are important reagents in organic chemistry, especially in the producing of naturally occurring products, compounds with biological and pharmacological activity [7-8]. In recent years, we have confirmed a one-pot method for the preparation of organophosphorus compounds [9-15].

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, antifungal, antiinflammatory, and antihypertensive [16-20]. Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multistep in nature [21-26]. The most general method involves the cyclization of diacylhydrazides with a variety of reagents, such as thionyl chloride, phosphorus oxychloride, 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 [27-32].

Ultrasound irradiation, an efficient and innocuous technique for reagent activation in the synthesis of inorganic compounds [33-38], organic compounds and in particular heterocyclic compounds, has been applied with success, milder reaction condition, and higher yields in comparison to the classical methods [39–41]. Ultrasound-promoted synthesis has attracted much attention during the past few decades. One advantage of using cavitation as an energy source to promote organic reactions includes shorter reaction times [42]. During the rarefaction cycle in the cavitation process, the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle. These rapid and violent implosions generate short-lived regions with temperatures of roughly 5000 $^{\circ}$C, pressures of about 1000 atm and heating and cooling rates above 10 billion $^{\circ}$C/s. Such localized hot spots can be thought as micro reactors in which the energy of sound is transformed into a useful chemical form [42,45,46]. This procedure has been considered as a clean and useful protocol in organic synthesis compared with traditional methods, and the procedure is in general, more convenient [42].

There are very few reports in literature about application of ultrasound irradiation in Isocyanide-based multicomponent reactions. In continuation of our research program to find the effect of ultrasound irradiation on isocyanide-based multicomponent reactions [43,44], we wish to report a novel and efficient method for the synthesis of 1,3,4-oxadiazole derivatives (**4**) via an efficient condensation of aromatic carboxylic acids, acenaphthoquinone, and *(N*-isocyanimino)triphenylphosphorane under ultrasound irradiation (Scheme 1).

Scheme 1

2. Experimental

2.1. Apparatus, materials and measurements

(*N*-Isocyanimino)triphenylphosphorane (**3**) was prepared based on reported procedures [8,47]. Other starting materials and solvents were purchased from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to monitor the reactions are TLC and NMR. Melting points were determined on an Electrothermal 9100 apparatus. IR spectra (ν_{max}, cm^{-1}) were recorded on a Jasco 6300 FTIR spectrophotometer using KBr technique. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were recorded on a Bruker DRX- 250 Avance spectrometer at 250.0 and 62.5 MHz, respectively. Mass analyses were carried out using a Finnigan MAT-8430 mass spectrometer operating at an ionization potential of 70 eV. Preparative layer chromatography (PLC) plates were prepared from Merck silica gel (F_{254}) powder. 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.

2.2. General procedure for the synthesis of the title compounds in CH_3CN

A mixture of (*N*-isocyanimino)triphenylphosphorane (302 mg, 1.0 mmol), acenaphthoquinone (182 mg, 1.0 mmol), and aromatic carboxylic acid (1.0 mmol) in CH_3CN (10 mL) was stirred at for 24 h in room temperature. The solvent was removed under reduced pressure, and the viscous residue was purified by PLC [silica gel (F_{254}) powder; petroleum ether/ethyl acetate 4:1].

2.3. Ultrasound-promoted typical procedure for synthesis of title compounds

The carboxylic acid derivatives (1.0 mmol), acenaphthoquinone (182 mg, 1.0 mmol), (N isocyanimino)triphenylphosphorane (302 mg, 1.0 mmol) and CH_3CN (10 mL) were added into a

25 mL round bottomed flask. During the ultrasound irradiation, the temperature of the mixture was controlled with ice bath (temperature was maintained in room temperature). The reaction mixture was sonicated under 100 W for the period of time (The reaction was monitored by TLC) and the . The solvent was removed under reduced pressure, and the viscous residue was purified by PLC [silica gel (F_{254}) powder; petroleum ether/ethyl acetate 4:1]. The authenticity of the samples (**4a**-**4p**) was established by their ^{1}H NMR, ^{13}C NMR and MS.

2.4. Data spectra of products

*2.4.1. Compound **4a***

2-Hydroxy-2-(5-phenyl-1,3,4-oxadiazol-2-yl)-1(2H)-acenaphthylenone (**4a**, $C_{20}H_{12}N_2O_3$)

Yellow powder; yield 80%; R_f = 0.36 (petroleum ether/ethyl acetate 4:1); m.p.: 162–164 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 4.59 (br s, OH), 7.40–8.30 (m, 11CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d= 87.74 (C–OH), 122.56, 123.88, 126.97, 127.13, 128.79, 128.96, 129.07, 132.02, 132.85 (11CH of arom), 123.22, 127.80, 129.60, 135.12, 142.96 (5C of arom), 161.05, 166.13 (2C=N of oxadiazole), 198.51 (C=O) ppm; IR (KBr): ν_{max}= 3,366, 3,073, 1,718, 1,603, 1,448, 1,012 cm^{-1}; MS (EI, 20 eV): m/z (%) = 328 (M^+), 198 (16), 182 (34), 154 (83), 126 (100), 98 (28), 85 (28), 76 (39), 62 (38), 43 (45).

*2.4.2. Compound **4b***

2-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone(**4b**, $C_{20}H_{11}BrN_2O_3$)

Yellow powder; yield 78%; R_f = 0.33(petroleum ether/ ethyl acetate 4:1); m.p.: 151–153 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d= 4.57 (br s, OH), 7.57 (d, ^{3}JHH =8.3 Hz, 2CHarom), 8.03 (d,

^{3}JHH= 8.3 Hz, 2CHarom), 7.69–7.86, 8.09–8.30 (m, 6CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d= 86.50 (C–OH), 122.59, 123.96, 127.03, 128.51, 128.83, 129.08, 132.33, 132.94 (10CH of arom), 122.12, 126.80, 129.50, 130.98, 134.22, 140.25 (6C of arom), 164.02, 165.03 (2C=N of oxadiazole), 202.02 (C=O) ppm; IR (KBr): ν_{max} = 3,204, 3,077, 1,733, 1,600, 1,481, 1,007 cm^{-1}; MS (EI, 20 eV): m/z (%) = 407 (M^+), 198 (8), 182 (37), 154 (78), 126 (100), 98 (22), 85 (22), 75 (55), 62 (45), 50 (18).

*2.4.3. Compound **4c***

4-[5-(1,2-Dihydro-1-hydroxy-2-oxo-1-acenaphthylenyl)-1,3,4-oxadiazol-2-yl]benzonitrile (**4c**, $C_{21}H_{11}N_3O_3$)

Yellow powder; yield 73%; R_f= 0.30 (petroleum ether/ethyl acetate 4:1); m.p.: 161–163 °C; ^{1}H NMR (250.13 MHz,$CDCl_3$): d= 3.63 (s, OH), 7.71–8.33 (m, 10CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 77.31 (C–OH), 122.07, 127.13, 127.60, 128.45, 129.09, 132.62, 132.75 (10CH of arom), 109.98, 115.51, 124.00, 128.90, 133.02, 135.05, 143.03 (7C of arom), 161.03, 165.13 (2C=N of oxadiazole), 192.21 (C=O) ppm; IR (KBr): ν_{max} = 3,439, 3,209, 1,729, 1,604, 1,495, 1,014 cm^{-1}; MS (EI, 20 eV): m/z (%) = 353 (M^+), 197 (17), 182 (32), 154 (73), 130 (100), 126 (85), 101 (90), 75 (86), 62 (47), 50 (48), 42 (30).

*2.4.4. Compound **4d***

2-Hydroxy-2-[5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl]-1(2H)-acenaphthylenone(**4d**, $C_{21}H_{14}N_2O_3$)

Yellow powder; yield 83%; R_f = 0.36 (petroleum ether/ ethyl acetate 4:1); m.p.: 169–171 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 2.37 (s, CH_3), 4.50 (br s, OH), 7.26–8.30 (m, 10CHarom) ppm;

^{13}C NMR (62.53 MHz, $CDCl_3$): d = 21.21 (CH_3), 76.57 (C–OH), 122.06, 122.55, 124.29, 126.84, 127.58, 128.44, 128.78, 129.07, 132.60, 132.86 (10CH of arom),123.82, 128.81, 129.10, 130.91, 134.80, 143.35 (6C of arom), 164.18, 166.75 (2C=N of oxadiazole), 198.87 (C=O) ppm; IR(KBr): ν_{max} = 3,399, 3,073, 1,723, 1,603, 1,490, 1,073 cm^{-1}; MS (EI, 20 eV): m/z (%) = 342 (M^+), 198 (6), 182 (24), 154 (54), 126 (60), 105 (100), 91 (18), 76 (54), 62 (23), 50 (24).

*2.4.5. Compound **4e***

2-[5-(4-*tert*-Butylphenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone(**4e**, $C_{24}H_{20}N_2O_3$)

Yellow powder; yield 85%; R_f = 0.33 (petroleum ether/ ethyl acetate 4:1); m.p.: 176–178 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 1.30 (s, 3CH_3), 5.30 (br s, OH), 7.41 (d, ^{3}JHH = 8.3 Hz, 2CHarom), 7.98 (d, ^{3}JHH = 8.3 Hz, 2CHarom), 7.71–7.86, 8.05–8.20 (m, 6CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 31.03 (3CH_3), 35.03 (C), 76.60 (C–OH), 122.53, 123.74, 125.89, 126.79, 126.98, 128.70, 129.03, 132.73 (10CH of arom), 122.04, 128.43, 129.75, 130.88, 135.51, 142.33 (6C of arom), 164.28, 166.00 (2C=N of oxadiazole), 198.17 (C=O) ppm; IR (KBr): ν_{max} = 3,209, 2,965, 1,738, 1,614, 1,495, 1,010 cm^{-1}; MS (EI, 20 eV): m/z (%) = 384 (M^+), 182 (11), 163 (25), 148 (14), 120 (38), 103 (17), 91 (73), 76 (35), 57 (18), 43 (100).

*2.4.6. Compound **4f***

2-[5-(3-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone(**4f**, $C_{20}H_{11}ClN_2O_3$)

Yellow powder; yield 76%; R_f = 0.30 (petroleum ether/ ethyl acetate 4:1); m.p.: 174–176 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 4.06 (br s, OH), 7.33–8.29 (m, 10CHarom) ppm; ^{13}C NMR

(62.53 MHz, $CDCl_3$):d = 77.25 (C–OH), 122.06, 123.98, 125.24, 127.02, 128.44, 129.09, 130.34, 132.09, 132.62, 132.94 (10CH of arom), 122.59, 128.83, 129.50, 133.82, 135.12, 148.62 (6C of arom), 158.50, 164.82 (2C=N of oxadiazole), 198.27 (C=O) ppm; IR (KBr): ν_{max} = 3,379, 3,080, 1,718, 1,602, 1,551, 1,068 cm^{-1}; MS (EI, 20 eV): m/z (%) = 362 (M^+), 197 (18), 182 (44), 154 (95), 126 (100), 98 (23), 85 (19), 75 (47), 62 (34), 50 (17).

*2.4.7. Compound **4g***

2-Hydroxy-2-[5-(3-phenoxyphenyl)-1,3,4-oxadiazol-2-yl]-1(2H)-acenaphthylenone(**4g**, $C_{26}H_{16}N_2O_4$)

Yellow powder; yield 72%; R_f = 0.26 (petroleum ether/ ethyl acetate 4:1); m.p.: 153–155 °C; ^1H NMR (250.13 MHz, $CDCl_3$): d = 4.81 (br s, OH), 6.96–8.29 (m, 15CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$):d = 85.02 (C–OH), 117.19, 119.14, 121.80, 122.05, 123.88, 123.97, 126.95, 128.77, 129.04, 129.95, 130.45, 130.92, 132.84 (15CH of arom), 122.52, 128.44, 129.62, 135.22, 145.30, 156.20, 157.85 (7C of arom), 165.45, 164.71 (2C=N of oxadiazole), 198.17 (C=O) ppm; IR(KBr): ν_{max} = 3,307, 3,082, 1,743, 1,563, 1,485, 1,225 cm^{-1}; MS (EI, 20 eV): m/z (%) = 420 (M^+), 214 (27), 197 (29), 182 (80), 154 (80), 126 (100), 98 (21), 85 (15), 76 (29), 62 (29), 50 (22).

*2.4.8. Compound **4h***

2-[5-[4-(Bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone (**4h**, $C_{21}H_{13}BrN_2O_3$)

Yellow powder; yield 82%; R_f = 0.33 (petroleum ether/ ethyl acetate 4:1); m.p.: 163–165 °C; ^1H NMR (250.13 MHz, $CDCl_3$): d = 4.46 (s, CH_2), 4.98 (br s, OH), 7.43 (d, ^3JHH = 8.3 Hz,

2CHarom), 7.90 (d, ^{3}JHH = 8.3 Hz, 2CHarom), 7.70–7.86, 7.99–8.29 (m, 6CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$):d = 32.09 (CH_2), 76.77 (C–OH), 122.56, 123.89, 126.95, 127.55, 129.07, 129.61, 132.62, 132.87 (10CH of arom), 123.10, 128.44, 128.79, 130.92, 135.24, 141.80 (6C of arom), 165.12, 166.22 (2C=N of oxadiazole), 198.15 (C=O) ppm; IR (KBr): ν_{max} = 3,343, 3,072, 1,717, 1,603, 1,486, 1,012 cm^{-1}.

*2.4.9. Compound **4i***

2-Hydroxy-2-[5-(1-naphthalenyl)-1,3,4-oxadiazol-2-yl]-1(2H)-acenaphthylenone(**4i**, $C_{24}H_{14}N_2O_3$)

Yellow powder; yield 75%; R_f = 0.36 (petroleum ether/ ethyl acetate 4:1); m.p.: 154–156 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 4.84 (br s, OH), 7.42–9.07 (m, 13CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$):d = 76.39 (C–OH), 122.60, 124.67, 125.95, 126.71, 126.96, 128.22, 128.59, 128.75, 128.79, 129.08, 132.88 (13CH of arom), 123.91, 128.35, 129.90, 131.92, 133.80, 135.22, 142.26 (7C of arom), 162.32, 166.25 (2C=N of oxadiazole), 198.17 (C=O) ppm; IR (KBr): ν_{max} = 3,433, 3,186, 1,741, 1,604, 1,538, 1,089 cm^{-1}.

*2.4.10. Compound **4j***

2-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone(**4j**, $C_{20}H_{11}ClN_2O_3$)

Yellow powder; yield 72%; R_f = 0.30 (petroleum ether/ ethyl acetate 4:1); m.p.: 169–171 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 4.58 (br s, OH), 7.77 (d, ^{3}JHH = 8.3 Hz, 2CHarom), 8.24 (d, ^{3}JHH = 8.3 Hz, 2CHarom), 7.40–7.73, 7.83–8.13 (m, 6CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 83.23 (C–OH), 122.07, 122.58, 128.40, 128.45, 129.09, 129.37, 132.63, 132.94

(10CH of arom), 123.95, 127.02, 128.83, 135.02, 137.52, 138.45 (6C of arom), 164.12, 165.23 (2C=N of oxadiazole), 202.12 (C=O) ppm; IR (KBr): ν_{max} = 3,227, 3,022, 1,732, 1,604, 1,486, 1,078 cm^{-1}.

*2.4.11. Compound **4k***

2-[5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone(**4k**, $C_{20}H_{11}FN_2O_3$)

Yellow powder; yield 75%; R_f = 0.33 (petroleum ether/ ethyl acetate 4:1); m.p.: 156–158 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 4.40 (s, OH), 7.10–8.31 (m, 10CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$):d = 82.65 (C–OH), 116.38 (d, $^2J_{CF}$ = 20.1 Hz, 2CH of arom), 122.06, 122.55, 128.44, 129.09, 132.62 (6CH of arom), 129.53 (d, $^3J_{CF}$ = 12.5 Hz, 2CH of arom), 123.93, 127.00, 128.94, 135.02, 140.74 (5C of arom), 160.52 (d, $^1J_{CF}$ = 252.0 Hz, C of arom), 164.48, 166.53 (2C=N of oxadiazole), 189.51 (C=O) ppm; IR (KBr): ν_{max} = 3,375, 3,082, 1,725, 1,606, 1,497, 1,013 cm^{-1}.

*2.4.12. Compound **4l***

2-Hydroxy-2-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]-1(2H)-acenaphthylenone(**4l**, $C_{21}H_{14}N_2O_3$)

Yellow powder; yield 80%; R_f = 0.36 (petroleum ether/ ethyl acetate 4:1); m.p.: 170–172 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 2.37 (s, CH_3), 4.30 (br s, OH), 7.20–8.29 (m, 10CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 21.61 (CH_3), 76.64 (C–OH), 122.05, 123.81, 127.07, 128.44, 129.05, 129.64, 132.61, 132.80 (10CH of arom), 122.52, 128.60, 128.75, 126.89, 135.22,

142.85 (6C of arom), 162.08, 164.13 (2C=N of oxadiazole), 198.10 (C=O) ppm; IR (KBr): ν_{max} = 3,355, 3,068, 1,725, 1,603, 1,498, 1,012 cm^{-1}.

*2.4.13. Compound **4m***

2-Hydroxy-2-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]-1(2H)-acenaphthylenone(**4m**, $C_{21}H_{14}N_2O_4$)

Yellow powder; yield 68%; R_f = 0.26 (petroleum ether/ ethyl acetate 4:1); m.p.: 195–197 °C; ^1H NMR (250.13 MHz, $CDCl_3$): d = 3.84 (s, CH_3), 4.33 (s, OH), 6.85–8.31 (m, 10CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 55.55 (OCH_3), 77.55 (C–OH), 114.40, 122.54, 123.92, 126.92, 128.93, 128.95, 132.50, 132.89 (10CH of arom), 122.54, 128.86, 131.04, 135.22, 140.04, 158.82 (6C of arom), 164.08, 166.53 (2C=N of oxadiazole), 194.51 (C=O) ppm; IR (KBr): ν_{max} = 3,244, 3,083, 1,739, 1,614, 1,500, 1,185 cm^{-1}.

*2.4.14. Compound **4n***

2-[5-(3,5-Dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone(**4n**, $C_{22}H_{16}N_2O_5$)

Yellow powder; yield 67%; R_f = 0.20 (petroleum ether/ ethyl acetate 4:1); m.p.: 168–170 °C; ^1H NMR (250.13 MHz, $CDCl_3$): d = 3.80 (s, $2OCH_3$), 4.43 (s, OH), 6.56–8.30 (m, 9CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 55.64 ($2OCH_3$), 87.00 (C–OH), 105.00, 107.05, 122.04, 123.94, 128.43, 132.59, 132.84 (9CH of arom), 124.75, 127.00, 131.04, 135.03, 142.10, 162.15 (7C of arom), 164.02, 166.43 (2C=N of oxadiazole), 189.51 (C=O) ppm; IR (KBr): ν_{max} = 3,380, 3,094, 1,725, 1,604, 1,463, 1,162 cm^{-1}.

*2.4.15. Compound **4o***

2-Hydroxy-2-[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]-1(2H)-acenaphthylenone(**4o**, $C_{21}H_{14}N_2O_3$)

Yellow powder; yield 72%; R_f = 0.34 (petroleum ether/ ethyl acetate 4:1); m.p.: 154–156 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 2.57 (s, CH_3), 4.09 (br s, OH), 7.06–8.64 (m, 10CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 22.32 (CH_3), 77.70 (C–OH), 122.06, 126.06, 126.98, 128.44, 129.09, 129.13, 131.50, 132.61, 132.80 (10CH of arom), 123.82, 128.60, 131.65, 132.00, 138.62, 140.35 (6C of arom), 164.18, 166.73 (2C=N of oxadiazole), 198.03 (C=O) ppm; IR (KBr): ν_{max} = 3,416, 3,072, 1,725, 1,604, 1,491, 1,014 cm^{-1}.

*2.4.16. Compound **4p***

2-[5-(3,4-Dimethylphenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxy-1(2H)-acenaphthylenone(**4p**, $C_{22}H_{16}N_2O_3$)

Yellow powder; yield 70%; R_f = 0.32 (petroleum ether/ ethyl acetate 4:1); m.p.: 167–169 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): d = 2.26, 2.28 (s, $2CH_3$), 4.42 (br s, OH), 7.07–8.75 (m, 9CHarom) ppm; ^{13}C NMR (62.53 MHz, $CDCl_3$): d = 19.65, 19.93 ($2CH_3$), 80.00 (C–OH), 122.05, 122.54, 126.89, 128.43, 128.59, 128.85,130.16, 132.61, 132.75 (9CH of arom), 122.05, 123.92, 127.50, 128.05, 129.02, 135.32, 145.90 (7C of arom), 164.18, 166.33 (2C=N of oxadiazole), 188.07 (C=O) ppm; IR (KBr): ν_{max} = 3,376, 3,083, 1,721, 1,603, 1,494, 1,184 cm^{-1}.

3. Results and Discussion

To achieve suitable conditions for the synthesis of disubstituted 1,3,4-oxadiazole derivatives (**4**), various reaction conditions have been investigated in the reaction of benzoic acid (**1a**), acenaphthoquinone (**2**), (*N*-isocyanimino)triphenylphosphorane (**3**) as a model reaction.

3.1. Effects of the solvents under ultrasound irradiation

To optimize the reaction conditions using different solvents (DMF, CH_2Cl_2, CH_3CN, CH_3OH, C_2H_5OH and 1,4-dioxane), were variably investigated in the synthesis of (**4a**) as model compound. The best result was obtained by the reaction of benzoic acid (1 mmol), acenaphthoquinone (1 mmol), (*N*-isocyanimino)triphenylphosphorane (1 mmol) in CH_3CN by ultrasound irradiation (100 W) to produce **(4a)** in 15 minutes with 93% yield (Table 1, entry 3). Dichloromethane, methanol and ethanol afforded moderate yields of desired products but took comparatively longer reaction time (Table 1, entries 2, 4 and 5). When the reaction was performed in DMF, and dioxane, unfortunately, the desired product was only obtained in 47% and 54% yield, respectively (Table 1, entries 1 and 6).

In order to verify the effect of ultrasound irradiation, the reaction was also performed in mentioned solvents by high stirring alone under silent condition (Table 1). As shown in Table 1, in all cases, the experimental results show that the yields of the products are lower than sonication within very longer time. Based on the results of this study, it's clear that the ultrasound improves the yields of products. With these results in hand, CH_3CN was chosen as solvent of reaction.

Table 1

3.2. Comparison of ultrasonic irradiation power

In order to verify the effect of irradiation power, the reaction was also performed in 50, 100, and 150 W. When the power was 100 W, the yield of 4a (93%) (Table 2, entry 2) was better than that with 50 W irradiation within 15 min (71%, Table 2, entry 1). With increase of irradiation power from 100 to 150 W (Table 2, entries 2, 3), the reaction yield did not change a considerable amount (93% in the similar time). The results are shown that there is an optimum power for effective synthesis of 4a in the power of 100 W.

Table 2

3.3. High efficiency and generality of synthesis by ultrasound irradiation

After detecting more efficient solvent (CH_3CN), and power (100 W) to delineate the role of ultrasound, this method was examined by the reaction of several substituted benzoic acids, acenaphthoquinone and (*N*-isocyanimino)triphenylphosphorane with and without ultrasonic irradiation at the same temperature in CH_3CN (Table 3). 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. The results in Table 3 show that ultrasound is much more efficient than magnetic stirring. Clearly, sluggish reactions were observed under conventional conditions and longer reaction time was required to achieve better yield. However, to our delight, ultrasound irradiation efficiently accelerated the reaction and markedly shortened the reaction time. Thus, ultrasonic irradiation was found to have beneficial effect on the synthesis of disubstituted 1,3,4-oxadiazoles which was superior to the traditional method with respect to yield, reaction time. To the best of our knowledge, this new

procedure provides the first example of an efficient and ultrasound-promoted three-component approach for the synthesis of disubstituted 1,3,4-oxadiazole derivatives.

3.4. Aspects of acceleration mechanism under irradiation of ultrasound

Sonochemistry can be defined as chemistry in a liquid medium in presence of pressure waves. The increasing interest for sonochemistry is due to the positive chemical and mechanical effects that can be observed when ultrasonic waves propagate in a liquid medium. Collapsing bubbles are generated, localized ‘‘hot spots” with a transient high temperature and pressures are formed, inducing molecular fragmentation, and highly reactive species are locally produced, which are responsible for the chemical effects of ultrasound on homogeneous solutions. In the some case, sonication can probably provide more efficient stirring [48-49]. All of these can cause the reaction to take place rapidly. With this case in mind, we turned our attention to the role of ultrasound irradiation in reaction mechanism. The suggested mechanism for the formation of products (**4a**–**4p**) is illustrated in Scheme 2. On the basis of the chemistry of isocyanides under ultrasonic irradiation condition, it is reasonable to assume that the first step may involve nucleophilic addition of (*N*-isocyanimino)triphenylphosphorane (**3**) to acenaphthoquinone (**2**), which is facilitated by its protonation with

Table 3

Scheme 2

the acid (**1**), leading to nitrilium intermediate (**6**). This intermediate may be attacked by the conjugate base of acid 1 to form 1:1:1 adduct (**7**). This adduct may undergo intramolecular aza-Wittig reaction of the iminophosphorane moiety with the ester carbonyl to afford the isolated sterically congested 1,3,4-oxadiazole derivatives (**4**) by elimination of triphenylphosphine oxide (**5**) from intermediate (**8**). 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. We believed that 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. As is known, deprotonation of the acid and the formation of *O*-centered nucleophiles occurred very slowly in the absence of ultrasound conditions. Moreover, the use of ultrasonic irradiation enabled the reaction to proceed smoothly under mild conditions even without the use of inert atmosphere.

Table 2

To the best of our knowledge, this new procedure provides the first example of an efficient and ultrasound-promoted approach for the synthesis of disubstituted 1,3,4-oxadiazole derivatives. This method is the most simple and convenient and would be applicable for the synthesis of different types of 1,3,4-oxadiazoles. The structures of all the synthesized compounds were established by their IR, Mass, ^{13}C NMR and ^{1}H NMR.

4. Conclusion

In conclusion, we have developed a new general and convenient method for synthesis of a series of 1,3,4-oxadiazole derivatives in high yields under ultrasound irradiation. To the best of our knowledge, this new procedure provides the first example of an efficient method for the synthesis of fully substituted 1,3,4-oxadiazole derivatives under ultrasound irradiation. The method leads to a series of disubstituted 1,3,4-oxadiazole bearing different aryl groups. Ultrasounds induce a remarkable acceleration for these reactions, the reaction times decreasing dramatically and the yields increasing considerably.

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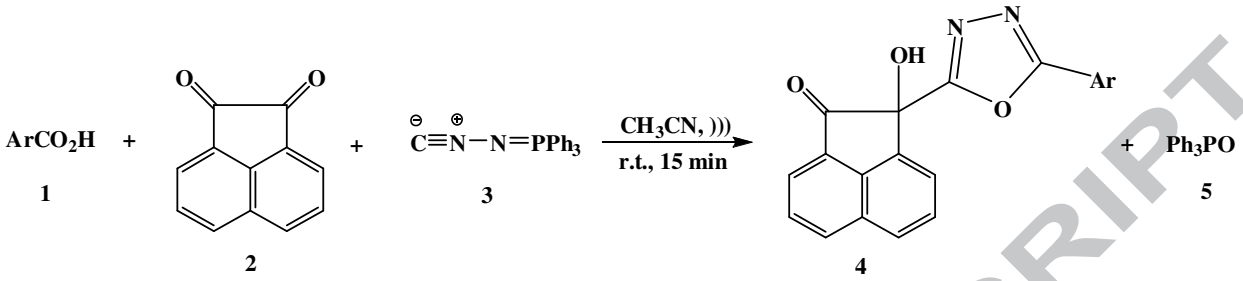
Scheme 1: Synthesis of disubstituted 1,3,4-oxadiazole derivatives under ultrasound irradiation.



Scheme 2. Probable mechanism for synthesis of disubstituted 1,3,4-oxadiazole derivatives.

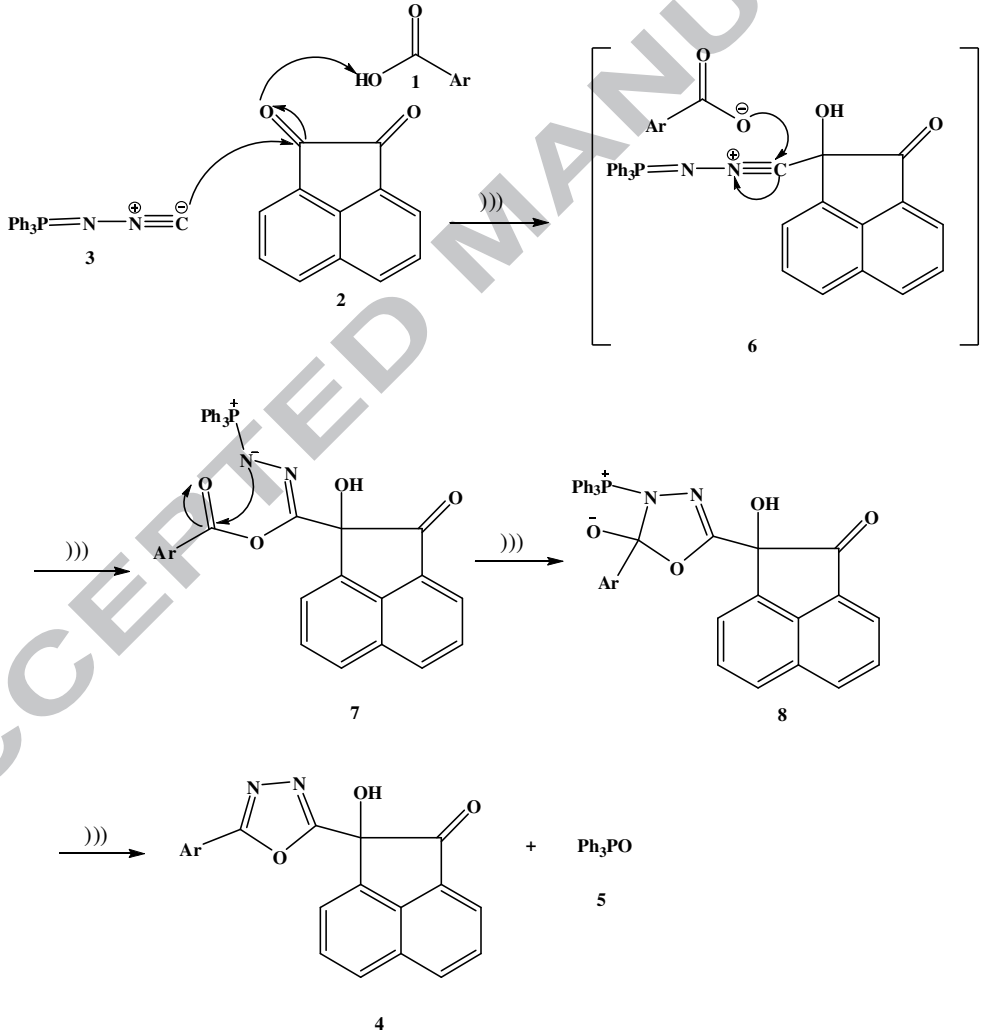


Table 1
The effect of reaction condition on the synthesis of **4a** under various conditions.

Entry	Solvent	With sonication[a]		Without sonication[b]	
		Time (min)	Yield[c] (%)	Time (h)	Yield[c] (%)
1	DMF	115	47	24	31
2	CH_2Cl_2	120	75	24	59
3	CH_3CN	15	93	24	80
4	Methanol	135	62	24	41
5	Ethanol	125	78	24	62
6	1,4-dioxane	110	54	24	38

[a] Reaction conditions: Reaction of (*N*-isocyanimino)triphenylphosphorane (1.0 mmol), acenaphthoquinone (1.0 mmol), and benzoic acid (1.0 mmol) in different solvents and ultrasonic power of 100 W for various times.
[b] Reaction condition: Reaction of (*N*-isocyanimino)triphenylphosphorane (1.0 mmol), acenaphthoquinone (1.0 mmol), and benzoic acid in different solvents at room temprature under high stirring condition for 24 hours.
[c] Isolated yields.

Table 2
The synthesis of **4a** under ultrasound irradiation in various frequencies.

Entry	Power (W)	Time (min)	Yield (%)
1	50	15	71
2	100	15	93
3	150	15	93

Table 3
Synthesis of **4a**–**4p** in CH_3CN with or without ultrasound irradiation.

Entry	Product	Ar	With sonication[a]	Without sonication[b]
			Yield[c] (%)	Yield[c] (%)
1	4a	C_6H_5	93	80
2	4b	4-BrC_6H_4	91	78
3	4c	4-CNC_6H_4	88	73

4	4d	3-MeC_6H_4	96	83
5	4e	4-*t*-BuC_6H_4	98	85
6	4f	3-ClC_6H_4	92	76
7	4g	3-$PhOC_6H_4$	89	72
8	4h	4-Br-$CH_2C_6H_4$	96	82
9	4i	$C_{10}H_7$	91	75
10	4j	4-Cl-C_6H_4	92	72
11	4k	4-FC_6H_4	90	75
12	4l	4-MeC_6H_4	94	80
13	4m	4-$MeOC_6H_4$	85	68
14	4n	3,5-di$MeOC_6H_3$	89	67
15	4o	2-MeC_6H_4	93	72
16	4p	3,5-diMeC_6H_3	91	70

[a] Reaction condition: Reaction of (*N*-isocyanimino)triphenylphosphorane (302 mg, 1.0 mmol), acenaphthoquinone (182 mg, 1.0 mmol), and aromatic carboxylic acid (1.0 mmol) in CH_3CN under ultrasound irradiation for 15 minutes.
[b] Reaction condition: Reaction of (*N*-isocyanimino)triphenylphosphorane (302 mg, 1.0 mmol), acenaphthoquinone (182 mg, 1.0 mmol), and aromatic carboxylic acid (1.0 mmol) in CH_3CN at room temperature in high stirring condition for 24 hours.
[c] Yields of isolated products.

- The best results were obtained in CH_3CN by ultrasound (100 W) in 15 minutes.
- The results show that ultrasound is much more efficient than magnetic stirring.
- The products were synthesized and characterized by melting point, IR, NMR and MS.
- We have developed a convenient method for synthesis of 1,3,4-oxadiazoles.