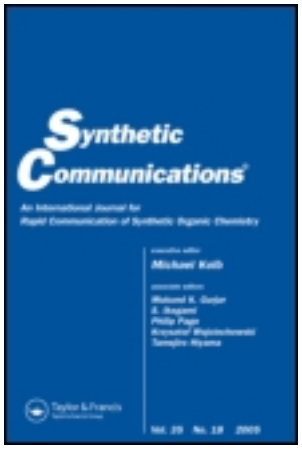

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One-Pot Efficient Synthesis of Fully Substituted 1,3,4-Oxadiazole Derivatives from (N-Isocyanimino)triphenylphosphorane, Carboxylic Acids, and Aromatic Bis-Aldehydes

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ONE-POT EFFICIENT SYNTHESIS OF FULLY SUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES FROM (*N*-ISOCYANIMINO)TRIPHENYLPHOSPHORANE, CARBOXYLIC ACIDS, AND AROMATIC BIS-ALDEHYDES

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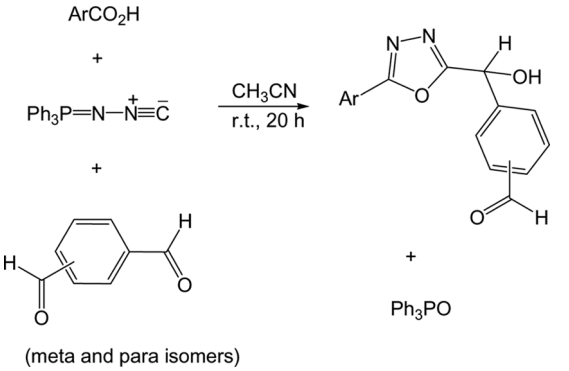
[2]*Young Researchers Club, Islamic Azad University, Zanjan Branch, Zanjan, Iran*

GRAPHICAL ABSTRACT



Abstract *Reactions of (*N*-isocyanimino)triphenylphosphorane with aromatic bis-aldehydes (isophthalaldehyde and terphthalaldehyde) in the presence of aromatic (or heteroaromatic) carboxylic acids proceed smoothly at room temperature and in neutral conditions to afford sterically congested 1,3,4-oxadiazole derivatives in good yields. The reaction proceeds smoothly and cleanly under mild conditions, and no side reactions were observed.*

Keywords Aromatic carboxylic acid; aza-Wittig reaction; heteroaromatic carboxylic acid; (*N*-isocyanimino)triphenylphosphorane; 1,3,4-oxadiazole

INTRODUCTION

Organophosphorus compounds[1–4] have been extensively employed in organic synthesis as useful reagents, as well as ligands, in a number of transition-metal catalysts.[3] Iminophosphoranes are important synthetic intermediates in organic chemistry, especially in the preparation of naturally occurring products and compounds

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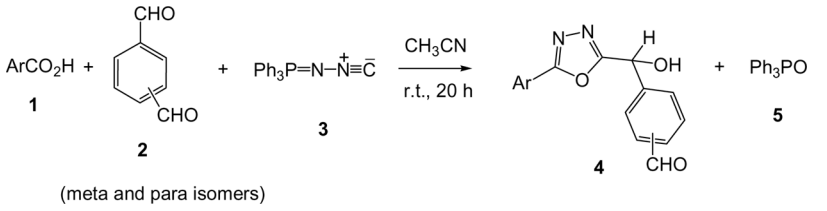
with biological and pharmacological activity.[5–11] In the fast few years, several preparative procedures have been reported for the preparations and synthetic applications of iminophosphoranes.[5–13] The unique synthetic potential of iminophosphoranes results from the presence of electron-rich nucleophilic nitrogen atoms and electrophilic phosphorus atoms as P^+-N^- bonds in their structures.[5] The structural properties of the P^+-N^- bond and its chemical reactivity have been investigated through theoretical, spectroscopic, and crystallographic investigations.[5,12,13] The presence of the P^+-N^- bond in the iminophosphorane structure is a factor of essential mechanistic importance in their applications as *aza*-Wittig reagents.[5] The intramolecular *aza*-Wittig reaction has attracted attention recently because of several applications for the preparation of nitrogen-containing heterocyclic compounds, which can result from the rapid progress in the synthesis of iminophosphorane derivatives as starting materials.[5–11] There are several reports for the use of (*N*-isocyanimino)triphenylphosphorane **3** in the preparation of metal complexes[12,13] (Scheme 1). However, the role of (*N*-isocyanimino)triphenylphosphorane **3** in organic chemistry remains unexplored.[12,13] The (*N*-isocyanimino)triphenylphosphorane **3** is expected to have unique synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality.[12,13] In recent years, we have established a one-pot method for the preparation of organophosphorus compounds.[14–22] As part of our ongoing program to develop efficient and robust methods for the synthesis of heterocyclic compounds,[23–31] we sought to develop a convenient preparation of 1,3,4-oxadiazole derivatives **4a–j** from (*N*-isocyanimino)triphenylphosphorane **3**, bis-aldehydes (isophthalaldehyde and terphthalaldehyde) **2,** and aromatic (or heteroaromatic) carboxylic acids **1** in excellent yields under neutral conditions (Scheme 1).

1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides.[32–34] They constitute an important class of heterocyclic compounds with a wide range of pharmaceutical and biological activities, including antimicrobial, antifungal, anti-inflammatory, antihypertensive, analgesic, antibacterial, hypoglycemic, antimalarial, antitubercular, and antidepressant activities.[32–34] Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multistep in nature.[35–37] The most general method involves the cyclization of diacylhydrazides with a variety of reagents, such as thionyl chloride, phosphorous oxychloride, or sulfuric acid, usually under harsh reaction conditions.[38] A reliable and simple method has been reported by the Ramazani research group for the one-pot synthesis of 1,3,4-oxadiazole derivatives from carboxylic acids and (*N*-isocyanimino)triphenylphosphorane **3**.[24,31]

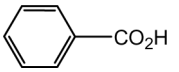
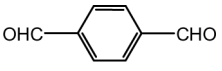
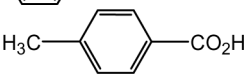
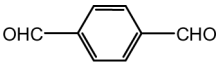
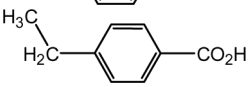
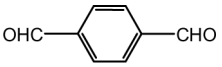
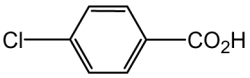
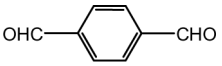
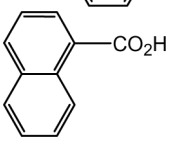
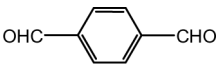
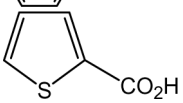
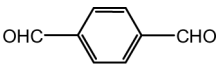
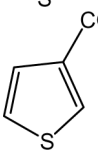
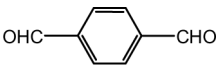
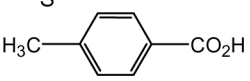
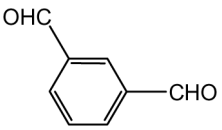
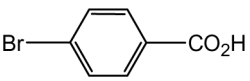
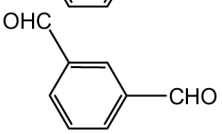
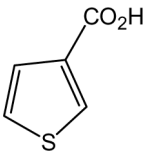
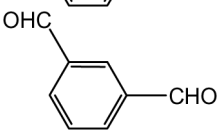


Scheme 1. Three-component synthesis of sterically congested 1,3,4-oxadiazole derivatives **4a–j** (see Table 1).

RESULTS AND DISCUSSION

In recent years, several synthetic methods have been reported for the preparation of (*N*-isocyanimino)triphenylphosphorane ($CNNPPh_3$) **3** (Scheme 1).[12,13] There are several reports for the use of (*N*-isocyanimino)triphenylphosphorane **3** in the synthesis of metal complexes.[12,13] However, application of **3** in the synthesis of organic compounds is rare.[14–22] As part of our ongoing program to develop

Table 1. Synthesis of sterically congested 1,3,4-oxadiazole derivatives **4a–j** from carboxylic acid **1** and aromatic bis-aldehydes **2** in the presence of (*N*-isocyanimino)triphenylphosphorane **3** (see Scheme 1)

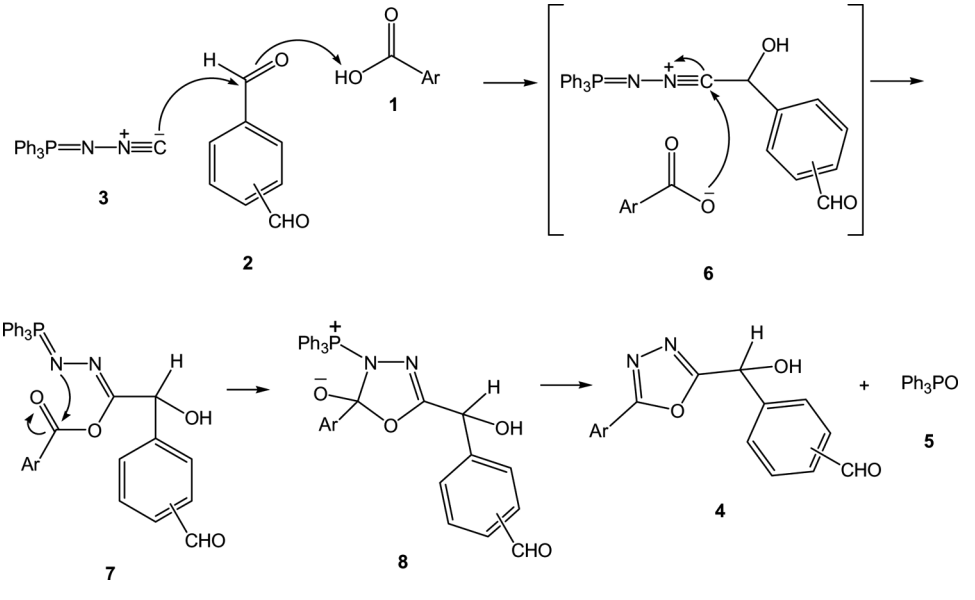
Carboxylic acid **1**	Bis-aldehyde **2**	Product **4**	Yield[a]
		**4a**	78
		**4b**	85
		**4c**	80
		**4d**	82
		**4e**	70
		**4f**	72
		**4g**	75
		**4h**	83
		**4i**	80
		**4j**	72

[a]Isolated yields.

efficient and robust methods for the preparation of heterocyclic compounds,[23–31] we sought to develop a convenient preparation of sterically congested 1,3,4-oxadiazole derivatives **4** from (*N*-isocyanimino)triphenylphosphorane **3**, bis-aldehydes (isophthalaldehyde and terphthalaldehyde) **2**, and aromatic (or heteroaromatic) carboxylic acids **1** in excellent yields under neutral conditions (Scheme 1). The carboxylic acid derivative **1** with bis-aldehyde (isophthalaldehyde and terphthalaldehyde) **2** and (*N*-isocyanimino)triphenylphosphorane **3** in CH_3CN react together in a 1:1:1 ratio at room temperature to produce sterically congested 1,3,4-oxadiazole derivatives **4** and triphenylphosphine oxide **5** (Scheme 1, Table 1). The reaction proceeds smoothly and cleanly under mild conditions, and no side reactions were observed. (Other aspects of these types multicomponent reactions are currently under investigation in our laboratory.)

The structures of the products were deduced from their infrared (IR), mass, ^{1}H NMR, and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4a** consisted of a broad singlet for the OH ($\delta = 3.26$, exchangeable by D_2O), a singlet for CH ($\delta = 6.80$), and a singlet for CH of aldehyde group ($\delta = 10.00$). The aryl groups exhibited characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 12 distinct resonances, and partial assignment of these resonances is given in the experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **4b–j** were similar to those of **4a**, except for the aromatic or heteroaromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

The suggested mechanism for the formation of products **4a–j** is illustrated in Scheme 2. On the basis of the chemistry of isocyanides, it is reasonable to assume that the first step may involve nucleophilic addition of the (*N*-isocyanimino)



Scheme 2. Proposed mechanism for the formation of sterically congested 1,3,4-oxadiazole derivatives **4a–j**.

triphenylphosphorane **3** to bis-aldehyde **2**, which facilitates its protonation with the acid **1**, leading to nitrilium intermediate **6**. This intermediate may be attacked by conjugate base of the acid **1** to form 1:1:1 adduct **7**. This adduct may undergo intramolecular aza-Wittig[23–29] reaction of iminophosphorane moiety with the ester carbonyl to afford the isolated sterically congested 1,3,4-oxadiazole derivatives **4** by removal of triphenylphosphine oxide **5** from intermediate **8**.

CONCLUSION

We believe that the reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazole derivatives **4** from (*N*-isocyanimino) triphenylphosphorane **3**, bis-aldehydes (isophthalaldehyde and terphthalaldehyde) **2** and aromatic (or heteroaromatic) carboxylic acids **1**. Its ease of workup, good yields, and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies.[39–49]

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions are thin-layer chromatography (TLC). TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco Fourier transform 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. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 20 eV. Flash chromatography columns were prepared from Merck silica-gel powder.

General Procedure

A mixture of (*N*-isocyanimino)triphenylphosphorane **3** (1.0 mmol), aromatic bis-aldehyde **2** (1.0 mmol), and carboxylic acid **1** (1.0 mmol) in CH_3CN (5 mL) was stirred at room temperature for 20 h. Then, the solvent was removed under reduced pressure, and the viscous residue was purified by flash column chromatography [silica-gel powder; petroleum ether–ethyl acetate (4:1)]. The solvent was removed under reduced pressure to give the products **4**. The characterization data of the compounds are given.

Selected Data

4-(Hydroxy(5-phenyl-1,3,4-oxadiazol-2-yl)methyl)benzaldehyde (4a). White crystals, mp 76–78 °C, yield 78%. IR (KBr) (υ_{max}, cm^{-1}): 3401, 2919, 1700, 1606, 1449, 1204, 1079. Anal. calcd. for $C_{16}H_{12}N_2O_3$: C,68.56; H, 4.32; N, 9.99%. Found: C, 68.51; H, 4.37; N, 9.92. ^{1}H NMR (250.13 MHz, DMSO-d_6) δ: 3.26 (1H, br s, OH), 6.80 (1H, s, CH), 7.25–8.05 (9H, m, H-Ar), 10.00 (1H, s, CHO).

^{13}C NMR (62.53 MHz, DMSO-*d*6) δ: 71.56 (CH); 131.58, 131.99, 133.97, 134.65, 136.77 (9CH of arom); 128.30, 140.99, 150.51 (3C of arom); 162.30 and 169.08 (2C=N, oxadiazole); 191.67 (C=O of aldehyde).

4-(Hydroxy(5-p-tolyl-1,3,4-oxadiazol-2-yl)methyl)benzaldehyde (4b). Yellow crystals, mp 91–93 °C, yield 85%. IR (KBr) (υ_{max}, cm^{-1}): 3389, 2922, 1700, 1607, 1480, 1202, 1068. Anal. calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52%. Found: C, 69.45; H, 4.74; N, 9.45. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ: 2.39 (3H, s, CH_3), 4.25 (1H, br s, OH), 6.23 (1H, s, CH), 7.25–7.92 (8H, m, H-Ar), 10.02 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 21.66 (CH_3); 67.79 (CH); 126.99, 127.15, 129.78, 130.21 (8CH of arom); 129.18, 136.61, 142.86, 144.03 (4C of arom); 164.85 and 166.20 (2C=N of oxadiazole); 191.72 (C=O of aldehyde). MS *m*/*z*: 294 (M^+, 60), 159 (100), 133 (27), 119 (54), 105 (15), 91 (67), 77 (47), 57 (20), and 43 (24).

4-((5-(4-Ethylphenyl)-1,3,4-oxadiazol-2-yl)(hydroxy)methyl)benzaldehyde (4c). Yellow crystals, mp 77–79 °C, yield 80%. IR (KBr) (υ_{max}, cm^{-1}): 3396, 2919, 1699, 1607, 1498, 1206, 1048. Anal. calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09%. Found: C, 70.08; H, 5.20; N, 9.05. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ: 1.22 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3 of Et); 2.66 (2H, q, $^3J_{HH} = 7.2$ Hz, CH_2 of Et), 5.35 (1H, br s, OH), 6.23 (1H, s, CH); 7.24–7.86 (8H, m, H-Ar), 9.98 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 15.16 (CH_3 of Et); 28.89 (CH_2 of Et); 67.53 (CH); 127.08, 127.14, 128.23, 130.13 (8CH of arom); 124.49, 136.46, 144.35, 149.02 (4C of arom); 165.78 and 166.13 (2C=N of oxadiazole); 191.80 (C=O of aldehyde).

4-((5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)(hydroxy)methyl)benzaldehyde (4d). Yellow oil, yield 82%. IR (KBr) (υ_{max}, cm^{-1}): 3403, 2918, 1699, 1604, 1480, 1204, 1089. Anal. calcd. for $C_{16}H_{11}ClN_2O_3$: C, 61.06; H, 11.26; N, 8.90%. Found: C, 61.11; H, 11.19; N, 8.95. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ: 4.70 (1H, br s, OH), 6.25 (1H, s, CH), 7.27–7.90 (8H, m, H-Ar), 10.01 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 67.66 (CH); 127.12, 128.28, 129.50, 130.23 (8CH of arom); 121.53, 136.66, 138.59, 143.86 (4C of arom); 164.90 and 166.39 (2C=N of oxadiazole); 191.70 (C=O of aldehyd). MS *m*/*z*: 314 (M^+, 22), 294 (20), 179 (24), 156 (60), 139 (100), 111 (60), 91 (60), 69 (53), 57 (54) and 43 (59).

4-{Hydroxy[5-(2-naphthyl)-1,3,4-oxadiazol-2-yl}methyl]benzaldehyde (4e). Yellow crystals, mp 99–100 °C, yield 70%. IR (neat) (υ_{max}, cm^{-1}): 3412, 2920, 1694, 1607, 1458, 1205, 1069. Anal. calcd. for $C_{24}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48%. Found: C, 72.66; H, 4.34; N, 8.41. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ: 4.83 (1H, br s, OH), 6.31 (1H, s, CH), 7.37–9.03 (11H, m, H-Ar), 10.00 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 67.88 (CH); 124.75, 126.81, 127.19, 128.32, 128.73, 130.22 (11CH of arom); 125.83, 133.07, 133.72, 136.60, 144.04 (5C of arom); 162.20 and 169.80 (2C=N of oxadiazole); 191.74 (C=O of aldehyde).

4-{Hydroxyl[5-(2-thienyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (4f). Yellow oil, yield 72%. IR (neat) (υ_{max}, cm^{-1}): 3407, 2919, 1698, 1606, 1457, 1205, 1048. Anal. calcd. for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78%. Found: C, 58.77; H, 3.55; N, 9.70. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ: 4.82 (1H, br s, OH), 6.22 (1H, s, CH), 7.16–7.95 (7H, m, H-Ar), 10.08 (1H, s, CHO). ^{13}C NMR

(62.53 MHz, $CDCl_3$) δ: 67.84 (CH); 127.13, 128.21, 130.25, 130.42, 130.76 (7CH of arom); 124.87, 136.90, 143.81 (3C of arom); 160.50 and 165.95 (2C=N of oxadiazole); 191.60 (C=O of aldehyde).

4-{Hydroxyl[5-(3-thienyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (4g). Yellow oil, yield 75%. IR (neat) (υ_{max}, cm^{-1}): 3380, 2922, 1698, 1603, 1206, 1057. Anal. calcd. for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78%. Found: C, 58.80; H, 3.47; N, 9.72. ^1H NMR (250.13 MHz, $CDCl_3$) δ: 4.86 (1H, br s, OH), 6.23 (1H, s, CH), 7.25–8.05 (7H, m, H-Ar), 10.0 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 67.55 (CH); 125.87, 127.13, 127.66, 128.14, 130.19 (7CH of arom); 124.34, 136.55, 145.07 (3C of arom); 162.30 and 166.30 (2C=N of oxadiazole); 191.79 (C=O of aldehyde).

3-(Hydroxy(5-p-tolyl-1,3,4-oxadiazol-2-yl)methyl)benzaldehyde (4h). Yellow crystals, mp 10–105 °C, yield 83%. IR (KBr) (υ_{max}, cm^{-1}): 3384, 2918, 1700, 1608, 1499, 1049. Anal. calcd. for $C_{17}H_{14}N_2O_3$ (294.30): C, 69.38; H, 4.79; N, 9.52%. Found: C, 69.33; H, 4.85; N, 9.46. ^1H NMR (250.13 MHz, $CDCl_3$) δ: 2.39 (3H, s, CH_3), 4.34 (1H, br s, OH), 6.23 (1H, s, CH), 7.25–8.09 (8H, m, H-Ar), 10.03 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 21.66 (CH_3); 67.68 (CH); 126.99, 127.86, 129.62, 129.77, 130.03, 132.50 (8CH of arom); 127.30, 129.48, 136.82, 142.79 (4C of arom); 162.30 and 171.25 (2C=N of oxadiazole); 191.85 (C=O of aldehyde).

3-((5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)(hydroxy)methyl)benzaldehyde (4i). Yellow crystals, mp 133–135 °C, yield 80%. IR (KBr) (υ_{max}, cm^{-1}): 3408, 2919, 1700, 1604, 1466, 1204, 1059. Anal. calcd. for $C_{16}H_{11}BrN_2O_3$: C, 53.50; H, 3.09; N, 7.80%. Found: C, 53.55; H, 3.15; N, 7.73. ^1H NMR (250.13 MHz, $CDCl_3$) δ: 4.60 (1H, br s, OH), 6.25 (1H, s, CH), 7.59–8.09 (8H, m, H-Ar), 10.02 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 67.60 (CH); 127.62, 128.40, 129.69, 129.83, 132.45 (8CH of arom); 122.04, 126.97, 136.84, 138.89 (4C of arom); 165.00 and 166.57 (2C=N of oxadiazole); 191.82 (C=O of aldehyde).

3-{Hydroxyl[5-(3-thienyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (4j). Yellow oil, yield 72%. IR (KBr) (υ_{max}, c^{-1}): 3399, 2920, 1698, 1605, 1437, 1057. Anal. calcd. for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78%. Found: C, 58.67; H, 3.45; N, 9.75. ^1H NMR (250.13 MHz, $CDCl_3$) δ: 2.70 (1H, br s, OH), 6.20 (1H, s, CH), 7.25–8.35 (7H, m, H-Ar), 9.95 (1H, s, CHO). ^{13}C NMR (62.53 MHz, $CDCl_3$) δ: 66.96 (CH); 125.87, 127.13, 12.66, 130.19 (7CH of arom); 129.18, 136.61, 144.03 (3C of arom); 160.01 and 169.80 (2C=N of oxadiazole); 192.05 (C=O of aldehyde).

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