A simple and efficient approach for the synthesis of new 1,3,4-oxadiazoles via a two-component reaction of N-isocyaniminotriphenylphosphorane and electron-rich benzoic acid derivatives

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ABSTRACT
The reactions of electron-rich benzoic acid derivatives with N-isocyaniminotriphenylphosphorane proceed smoothly at room temperature to afford 2-aryl-1,3,4-oxadiazoles in high yields.

INTRODUCTION
Within the past decade, the resurgence of interest in multicomponent reactions (MCRs) has been driven, not only due to their convergent nature, superior atom economy, and straightforward experimental procedures but also because of their value to the pharmaceutical industry for construction of low molecular weight compound libraries through combinatorial strategies and parallel synthesis[1-4]. Isocyanide-based multicomponent condensation reactions (IMCRs) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of synthesis chemistry[5-10]. Since 1,3,4-oxadiazoles are an important class of heterocyclic compounds, they not only have considerable implications in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides but also a wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, and antihypertensive[11]. For the synthesis of 1,3,4-oxadiazole derivatives, several methods have been reported in the literature. It should be mentioned these methods are multi-step in nature[12-13]. The intramolecular version of the aza-Wittig-type reaction has attracted considerable attention recently because of its high potential for the...
synthesis of a wide variety of nitrogen heterocycles, which can be attributed, in good measure, to the rapid progress in the preparation of functionalized iminophosphoranes. The nucleophilicity at the nitrogen is a factor of essential mechanistic importance in the use of these iminophosphoranes as aza-Wittig reagents. Iminophosphoranes are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity\textsuperscript{[14-18]}. In recent years, several synthetic methods have been reported for the preparation of \( N \)-isocyaniminotriphenylphosphorane; 2)\textsuperscript{[19,20]}. There are several reports on the use of 2 in the synthesis of metal complexes\textsuperscript{[19,20]}. However, application of 2 in the synthesis of organic compounds is fairly rare\textsuperscript{[21-23]}. As part of our ongoing program to develop efficient and robust methods for the preparation of organic compounds\textsuperscript{[24-27]}, we sought to develop a convenient preparation of 2-aryl-1,3,4-oxadiazole derivatives 5a-5h. Herein, we report a two-component reaction, which, starting from simple and readily available electron-rich benzoic acid derivatives affords 2-aryl-1,3,4-oxadiazoles 5a-5h in a one-pot reaction with \( N \)-isocyaniminotriphenylphosphorane 2 (Scheme 1).

**RESULTS AND DISCUSSION**

Recently, 1,3,4-oxadiazoles have been the object of intense research in organic synthesis and medicinal chemistry, and several procedures have been reported for the synthesis of this heterocyclic compounds which are multi-step in nature\textsuperscript{[12,13]}

Herein, we describe a novel and straightforward approach for the synthesis of oxadiazoles via one-pot reaction of electron-rich benzoic acid derivatives and \( N \)-isocyaniminotriphenylphosphorane followed by a aza-Wittig cyclization in \( \text{CH}_2\text{Cl}_2 \) at ambient temperature in excellent yields (Scheme 1 and Figure and Table).

The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed. The mechanism of the reaction between the electron-rich benzoic acid derivative 1 and \( N \)-isocyaniminotriphenylphosphorane 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\textsuperscript{[11]}, 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

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**TABLE 1 : Synthesis of disubstituted 1,3,4-oxadiazole derivatives 5 (See scheme 1 and figure)**

<table>
<thead>
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<th>Compound</th>
<th>Z</th>
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<td>H</td>
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<td>5h</td>
<td>O</td>
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<td>N</td>
</tr>
</tbody>
</table>
Figure 1: Two-component synthesis of disubstituted 1,3,4-oxadiazole derivatives 5a-h (see table and text)

Scheme 2: Proposed mechanism for the formation of disubstituted 1,3,4-oxadiazole derivatives 5a-h
Intramolecular aza-Wittig reaction of iminophosphorane 4 would lead to the formation of 2-aryl-1,3,4-oxadiazoles 5 and triphenylphosphine oxide 6 (Scheme 2). The structures of the products 5a-h were deduced from their IR, Mass, $^1$H NMR, and $^{13}$C NMR spectra. For example the IR spectrum of 5a showed strong absorptions at 3071.86 (CH, aromatic); 1615.38 and 1500.02 (C=C, aromatic); 1238.46 and 746.15 (oxadiazole and aromatic parts) cm$^{-1}$ indicating the presence of the mentioned functionalities in its formula. The $^1$H NMR spectrum of 5a compound exhibited three signals readily recognized as arising from aromatic moiety [$\delta=7.18-7.26$ (d, 2 H, $^3$$J_{HH}$=7.5 Hz, arom.), $8.06-8.13$ (d, 2 H, $^3$$J_{HH}$ = 7.5 Hz, arom.)] and a CH of oxadiazole ring ($\delta=8.04$, s, 1 H). The $^1$H decoupled $^{13}$C NMR spectrum of 5a showed six distinct resonances 166.94(1C, oxadiazole) ; 163.43(d, 1C, $^1$$J_{CF}$=66.87Hz, arom); 152.61(1CH, oxadiazole), 129.41(d, 2CH, $^3$$J_{CF}$=8.75Hz, arom) 119.78(s,1C, arom), 116.5(d, 2CH, $^2$$J_{CF}$=22.5Hz arom) that are in agreement with the formula and structure of 5a. Partial assignment of these resonances is given in the spectral analysis section (See experimental section). The $^1$H and $^{13}$C NMR spectra of compounds 5b–h were similar to those of 5a, except for the aromatic or heteroaromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

In summary, we have found a new method for the preparation of 2-aryl-1,3,4-oxadiazoles 5 from the substituted electron-rich benzoic acid derivatives 1 and N-isocyananiminotriphenylphosphorane 2 in excellent yields under neutral conditions (Ramazani 1,3,4-oxadiazole synthesis). We believe that the reported method offers a mild and simple route for the preparation of these derivatives. Its ease of work-up and reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

**CONCLUSION**

In conclusion, we have developed an efficient and simple procedure for preparation of 2-aryl-1,3,4-oxadiazoles using electron-rich benzoic acid derivatives and N-isocyananiminotriphenylphosphorane. This method possesses very simple route and the reaction is carried out under neutral conditions. Further application of the use of this reagent in combination is under investigation.

**EXPERIMENTAL**

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. The elemental analyses were performed with an Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Jasco 6300 FTIR spectrometer. $^1$H and $^{13}$C NMR Spectra were recorded on a measured (CDCl$_3$ solution) with a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.5 MHz, respectively. All products are known and were characterized by IR, NMR and mass spectra. N-isocyananiminotriphenylphosphorane 2[28] were prepared based on known procedures.

**General procedure for the preparation of compounds 5**

To a magnetically stirred solution of N-isocyananiminotriphenylphosphorane 2 (0.302 g, 1 mmol) in dry CH$_2$Cl$_2$ (7mL), a solution of electron-rich benzoic acid derivatives 1 (1 mmol) in dry CH$_2$Cl$_2$ (4 mL) was added dropwise over 15 min. The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the product 5 was obtained. The characterization data of the compounds are given below:

2-(4-fluorophenyl)-1,3,4-oxadiazole (5a)

White crystal, m.p: 142.1°C (Yield 84%). $^1$H NMR (CDCl$_3$): 8.47(s, 1H, oxadiazole) ; 8.13-8.06(m, 2H, arom) ; 7.26-7.18 (m, 2H, arom). $^{13}$C NMR(62.5 MHz, CDCl$_3$) δ (ppm): 166.94(1C, oxadiazole) ; 163.43(d, 1C, $^1$$J_{CF}$=66.87Hz, arom) ;
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152.61 (1CH, oxadiazole), 129.41 (d, 2CH, J = 8.75Hz, arom) 119.78 (s, 1C, arom), 116.5 (d, 2CH, J = 22.5Hz, arom).

IR (neat): ν<sub>max</sub> = 3071.86, 2931.56, 1615.38, 1500.02, 1238.46, 846.15, 746.15.

MS, m/z (%): 41(5), 43(8), 57(10), 115(8), 152(31), 181(100), 221(12).

2-Biphenyl-2-yl-[1,3,4]oxadiazole (5e)

Viscose oil (Yield 80%). 1H NMR (CDCl₃): 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). 13C NMR (62.5 MHz, CDCl₃) δ (ppm): 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).

IR (neat): ν<sub>max</sub> = 3316.38, 3138.46, 2930.77, 1615.38, 1584.62, 1507.69, 1453.85, 1323.08, 1276.92, 746.15.

MS, m/z (%): 41(48), 43(81), 57(3), 77(5), 91(30), 149(33), 167(21), 180(45), 194(100), 208(62), 223(65), 241(58), 265(59), 266(15).

2-Naphthalen-2-yl-[1,3,4]oxadiazole (5g)

Yellow crystals, m.p: 149.8-150.0°C (Yield 72%). 1H NMR (CDCl₃): 8.15 (d, J<sub>HH</sub> = 1.6Hz, 2H, arom); 8.04-7.90 (m, 4H, arom); 7.62-7.59 (m, 2H, arom). 13C NMR (62.5 MHz, CDCl₃) δ (ppm): 167.83 (1C, oxadiazole); 150.96 (1CH, oxadiazole); 146.22, 138.57, 138.28, 105.79 (4C, arom); 132.76, 128.31, 127.08, 125.98, 123.39, 116.76, 113.64 (7CH, arom).

IR (neat): ν<sub>max</sub> = 3316.38, 3138.46, 2930.77, 1615.38, 1584.62, 1507.69, 1453.85, 1323.08, 1276.92, 746.15.

MS, m/z (%): 41(48), 43(81), 57(42), 77(7), 91(30), 149(33), 167(21), 180(45), 194(100), 208(62), 223(65), 241(58), 265(59), 266(15).

2-Naphthalen-2-yl-[1,3,4]oxadiazole (5f)

Yellow crystals, m.p: 149.8-150.0°C (Yield 72%). 1H NMR (CDCl₃): 8.15 (d, J<sub>HH</sub> = 1.6Hz, 2H, arom); 8.04-7.90 (m, 4H, arom); 7.62-7.59 (m, 2H, arom). 13C NMR (62.5 MHz, CDCl₃) δ (ppm): 167.83 (1C, oxadiazole); 150.96 (1CH, oxadiazole); 146.22, 138.57, 138.28, 105.79 (4C, arom); 132.76, 128.31, 127.08, 125.98, 123.39, 116.76, 113.64 (7CH, arom).

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MS, m/z (%): 41(48), 43(81), 57(42), 77(7), 91(30), 149(33), 167(21), 180(45), 194(100), 208(62), 223(65), 241(58), 265(59), 266(15).

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