

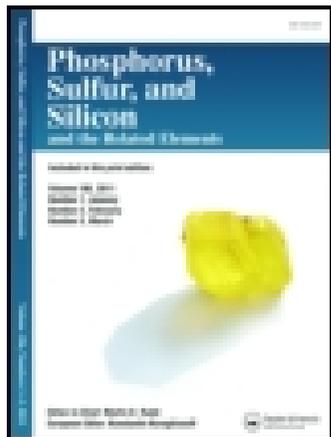
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### The Reaction of (N-Isocyanimino)triphenylphosphorane with Anthranilic Acid Derivatives: One-Pot Synthesis of 2-Substituted 1,3,4-Oxadiazoles via Intramolecular Aza-Wittig Reaction

Ali Ramazani <sup>a</sup> & Ali Souldozi <sup>b</sup>

<sup>a</sup> Chemistry Department , Zanzan University , Zanzan, Iran

<sup>b</sup> Chemistry Department , Islamic Azad University , Urmia Branch, Urmia, Iran

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## The Reaction of (*N*-Isocyanimino)triphenylphosphorane with Anthranilic Acid Derivatives: One-Pot Synthesis of 2-Substituted 1,3,4-Oxadiazoles via Intramolecular Aza-Wittig Reaction

Ali Ramazani<sup>1</sup> and Ali Souldozi<sup>2</sup>

<sup>1</sup>Chemistry Department, Zanjan University, Zanjan, Iran

<sup>2</sup>Chemistry Department, Islamic Azad University, Urmia Branch, Urmia, Iran

*The reaction of anthranilic acid derivatives with (N-isocyanimino)triphenylphosphorane proceeds smoothly at room temperature to afford 2-substituted 1,3,4-oxadiazoles via an intramolecular aza-Wittig reaction in excellent yields under neutral conditions. The structures of the products were deduced from their IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectra and mass spectrometry.*

**Keywords** Anthranilic acid derivatives; iminotriphenylphosphorane; intramolecular aza-Wittig reaction; (*N*-isocyanimino)triphenylphosphorane; 1,3,4-oxadiazole

### INTRODUCTION

Organophosphorus compounds<sup>1–5</sup> have been extensively employed in organic synthesis as useful reagents, as well as ligands, in a number of transition metal catalysts.<sup>3</sup> Iminophosphoranes are a class of special type of zwitterions, which bear a strongly nucleophilic electron-rich nitrogen. The electron distribution around the P<sup>+</sup>–N<sup>–</sup> bond and its consequent chemical implications have been probed and assessed through theoretical, spectroscopic, and crystallographic investigations.<sup>6–8</sup> The proton affinity of these iminophosphoranes can be used as a molecular guide to assess their utility as synthetic reagents and their function as ligands in coordination and organometallic chemistry.<sup>6–8</sup>

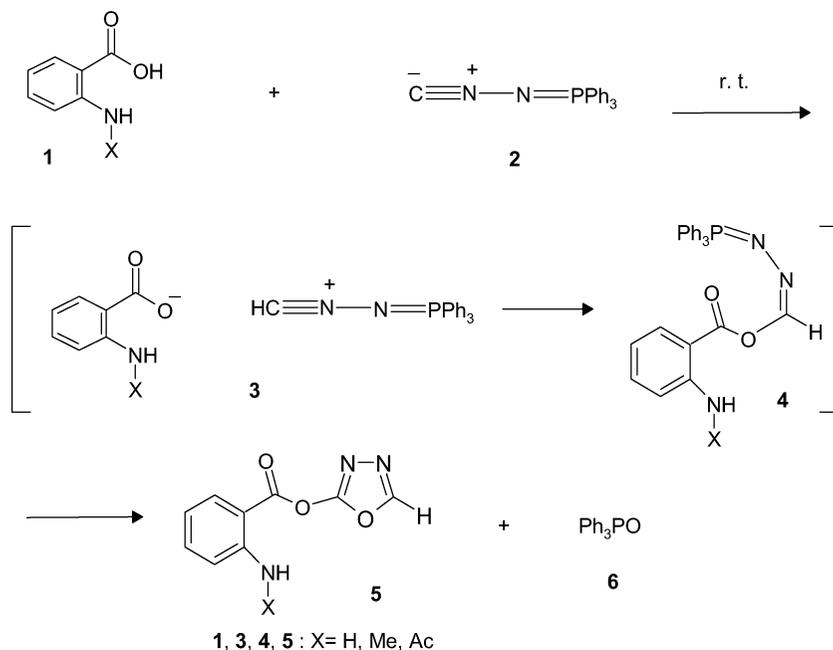
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Address correspondence to Ali Ramazani, Chemistry Department, Zanjan University, P.O. Box 45195-313, Zanjan, Iran. E-mail: aliramazani@gmail.com

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. Several interesting heterocyclization reactions involving iminophosphoranes have been reviewed.<sup>6</sup> These compounds can easily be converted through *aza*-Wittig reaction with isocyanates, carbon dioxide, or carbon disulfide into functionalized heterocumulenes that exhibit a rich chemistry of unusual synthetic promise.<sup>6</sup> 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, and compounds with biological and pharmacological activity.<sup>6</sup> However, the organic chemistry of (*N*-isocyanimino)triphenylphosphorane **2** remains almost unexplored.<sup>7,8</sup> (*N*-isocyanimino)triphenylphosphorane **2** is expected to have synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality.<sup>7,8</sup> In recent years, we have established a one-pot method for the synthesis of organophosphorus compounds (Ali Ramazani reaction).<sup>9–18</sup> As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,<sup>19–21</sup> we sought to develop a convenient preparation of 2-substituted 1,3,4-oxadiazoles **5** from anthranilic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** 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. They are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including antimicrobial, antifungal, antiinflammatory, and antihypertensive.<sup>22–26</sup> Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multistep in nature.<sup>27–32</sup> 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. 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.<sup>33–37</sup>



SCHEME 1

## RESULTS AND DISCUSSION

In the last years, several synthetic methods have been reported for the preparation of (*N*-isocyanimino)triphenylphosphorane (CNNPPh<sub>3</sub>) **2** (Scheme 1).<sup>7,8</sup> There are several reports for the use of (*N*-isocyanimino)triphenylphosphorane **2** in the synthesis of metal complexes.<sup>7,8</sup> However, application of **2** in the synthesis of organic compounds has not been reported. As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,<sup>19–21</sup> we sought to develop a convenient preparation of 2-substituted 1,3,4-oxadiazoles **5** from anthranilic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** (Scheme 1).

The anthranilic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** in dry CHCl<sub>3</sub> react together in a 1:1 ratio at room temperature to produce 2-substituted 1,3,4-oxadiazoles **5** and triphenylphosphine oxide **6** (Scheme 1). The reaction proceeds smoothly and cleanly under mild conditions. The mechanism of the reaction between the anthranilic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** has not been established experimentally. However, a possible explanation is proposed in Scheme 1. On

the basis of the well-established chemistry of isocyanides,<sup>19,20</sup> it is reasonable to assume that protonation of **2** by the anthranilic acid derivatives **1** followed by a quenching of the cationic center by the conjugate base of the carboxylic acid can generate the iminophosphorane **4**.<sup>6</sup> An intramolecular *aza*-Wittig<sup>6</sup> reaction of the iminophosphorane **4** would lead to formation of the 2-substituted 1,3,4-oxadiazoles **5** and triphenylphosphine oxide **6** (Scheme 1). The structures of the products **5a–c** were deduced from their IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The IR spectrum of **5a** showed strong adsorptions at 3431 and 3339 (NH<sub>2</sub>); 3039 (CH, aromatic); 1623 (C=C, aromatic); 1108 and 754 (oxadiazole and aromatic parts) cm<sup>-1</sup> indicating the presence of the mentioned functionalities in its formula. The <sup>1</sup>H NMR spectrum of **5a** compound exhibited six signals readily recognized as arising from amino group ( $\delta = 5.69$  [br. s, 2 H, NH<sub>2</sub>]), aromatic moiety ( $\delta = 6.73$  [d, 1 H, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, arom], 6.79 [t, 1 H, <sup>3</sup>J<sub>HH</sub> = 7.5 Hz, arom.], 7.75 [t, 1 H, <sup>3</sup>J<sub>HH</sub> Hz, arom.], 7.76 [d, 1 H, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, arom.]), and a CH of oxadiazole ring ( $\delta = 8.41$ , s, 1 H). The <sup>1</sup>H decoupled <sup>13</sup>C NMR spectrum of **5** showed eight distinct resonances ( $\delta = 116.28, 116.91, 127.99$  and  $132.79$  [4 CH, arom.];  $105.38$  and  $147.01$  [2 C, arom.];  $150.91$  [1 CH, oxadiazole];  $164.62$  [1 C, oxadiazole]) that are in agreement with the formula and structure of **5**. Partial assignment of these resonances is given in the spectral analysis section (see the Experimental section). We have also used other carboxylic acids (acetic acid, phthalic acid, maleic acid, chloroacetic acid, trichloroacetic acid, benzylic acid, 3,5-dinitrosalicylic acid, (2-hydroxyphenyl)acetic acid, 4-hydroxybenzoic acid, 3-hydroxybenzoic acid, salicylic acid, 4-aminobenzenesulfonic acid, 5-sulfosalicylic acid, nicotinic acid, 3-methoxyphenylacetic acid, 4-methoxyphenylacetic acid, diphenylacetic acid, 4-fluorobenzeneacetic acid, 3-phenylpropanoic acid, 4-chlorobenzeneacetic acid, benzenesulfonic acid, acetylenedicarboxylic acid, and methyl red) in this reaction, but no products were observed after 24 h. TLC indicated that the solution contained starting materials and some minor colored products.

## CONCLUSION

In summary, we have found a new method for the preparation of 2-substituted 1,3,4-oxadiazoles **5** from anthranilic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** in excellent yields under neutral conditions. We believe that the reported method offers a mild and simple route for the preparation of these derivatives. Its ease of workup

and reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

## EXPERIMENTAL

$^1\text{H}$  (250 MHz) and  $^{13}\text{C}$  (62.5 MHz) NMR measurements were recorded on a Bruker 250 spectrometer in  $\text{CDCl}_3$  with tetramethylsilane as internal standard. IR spectra were measured on a Shimadzu IR-460 spectrometer. Elemental analyses for C and H 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. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. (*N*-Isocyanimino) triphenylphosphorane **2** was prepared based on a reported procedure.<sup>7,8</sup> Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Flash chromatography columns were prepared from Merck silica gel powder.

### General Procedure for the Preparation of Compounds **4** and **5**

To a magnetically stirred solution of (*N*-isocyanimino)triphenylphosphorane<sup>7,8</sup> **2** (0.302 g, 1 mmol) in dry  $\text{CHCl}_3$  (4 mL) was added drop-wise a solution of anthranilic acid derivative **1** (1 mmol) in dry  $\text{CHCl}_3$  (4 mL) over 15 min. The mixture was stirred for 6 h at room temperature. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel; petroleum ether-ethyl acetate [10:2]). The solvent was removed under reduced pressure and the product **5** was obtained. The characterization data of the compounds are given below.

#### **2-(1,3,4-Oxadiazol-2-yl)Aniline 5a**

Light yellow crystals; Yield: 140 mg (86%); mp 145.3–145.4°C. IR (KBr):  $\nu = 3431, 3339, 3039, 2939, 2931, 2931, 1623, 1269, 1108, 754 \text{ cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 5.69$  (br. s, 2 H,  $\text{NH}_2$ ), 6.73 (s, 1 H, arom.), 6.79 (t, 1 H,  $^3J_{\text{HH}} = 7.5 \text{ Hz}$ , arom.), 7.75 (t, 1 H,  $^3J_{\text{HH}} = 7.8 \text{ Hz}$ , arom.), 7.76 (d, 1 H,  $^3J_{\text{HH}} = 6.0 \text{ Hz}$ , arom.), 8.41 (s, 1 H, oxadiazole).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 116.28, 116.91, 127.99$  and  $132.79$  (4 CH, arom.); 105.38 and 147.01 (2 C, arom.); 150.91 (1 CH, oxadiazole); 164.62 (1 C, oxadiazole). MS:  $m/z$  (%) 161 ( $\text{M}^+$ , 100%), 120 (50%), 105 (22), 92 (25), 90 (15), 78 (15), 77 (34), 65 (28), 63 (21), 58 (22), 55 (11), 52 (20), 51 (31), 50 (18), 43 (28), 41 (21).  $\text{C}_8\text{H}_7\text{N}_3\text{O}$  (161.06): Calcd (%): C 59.62, H 4.38, N 26.07; Found (%): C 59.57, H 4.34, N 26.14.

**Methyl-(2-[1,3,4]Oxadiazol-2-yl-Phenyl)-Amine 5b**

Yellow crystals; Yield: 90%, mp: 76.5–76.9°C. IR (KBr):  $\nu = 3353.85, 3107.69, 2930.77, 1623.08, 1523.08, 1284.62, 1176.92, 1115.38, 746.15$   $\text{cm}^{-1}$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.41 (s, 1H, oxadiazole); 7.81 (d, 1H,  $^3J_{\text{HH}} = 8.0$  Hz, arom); 7.53 (1H, NH of amine); 7.42 (t, 1H,  $^3J_{\text{HH}} = 7.8$  Hz, arom); 6.82–6.72 (m, 2H, arom); 3.04 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 164.77 (1C, oxadiazole); 150.75 (1CH, oxadiazole); 148.50 (1C, arom); 133.20, 128.24, 16.62, 115.12 (4CH, arom); 104.89 (1C, arom). MS:  $m/z$  (%) 175 ( $\text{M}^+$ , 10%), 167 (19), 149 (52), 105 (32), 91 (47), 75 (100), 57 (65), 43 (91), 41 (70).  $\text{C}_9\text{H}_9\text{N}_3\text{O}$  (175.07): Calcd (%): C 61.70, H 5.18, N 23.99; Found (%): C 61.59, H 5.11, N 24.10.

**N-(2-[1,3,4]Oxadiazol-2-yl-Phenyl)-Acetamide 5c**

Yellow crystals; Yield: 91%. mp: 134.5–135.2°C. IR (KBr):  $\nu = 3130.77, 2930.77, 1715.38, 1623.08, 1553.85, 1438.46, 1307.69, 1107.69$   $\text{cm}^{-1}$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 10.91 (s, 1H, NH); 8.78 (d, 1H,  $^3J_{\text{HH}} = 8.0$  Hz, arom); 8.50 (s, 1H, oxadiazole); 7.91 (d, 1H,  $^3J_{\text{HH}} = 8$  Hz, arom); 7.55–7.49 (m, 1H, arom); 7.20–7.14 (m, 1H, arom); 2.31 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 169.39 (1C, C = O, amide); 164.03 (1C, oxadiazole); 151.64 (1CH, oxadiazole); 138.56 (1C, arom); 133.28, 127.65, 123.09 and 120.61 (4 CH, arom); 109.67 (1C, arom). MS:  $m/z$  (%) 203 ( $\text{M}^+$ , 29%), 161 (100), 120 (24), 43 (17).  $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2$  (203.20): Calcd (%): C 59.11, H 4.46, N 20.68; Found (%): C 59.11, H 4.46, N 20.68.

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