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The reaction of (*N*-isocyanimino)triphenylphosphorane with benzoic acid derivatives: a novel synthesis of 2-aryl-1,3,4-oxadiazole derivatives

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Abstract—The reactions of benzoic acid derivatives with (*N*-isocyanimino)triphenylphosphorane proceed smoothly at room temperature to afford 2-aryl-1,3,4-oxadiazoles in high yields.

1. Introduction

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.[1–5]

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multi-step in nature.[6–11] 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.[12–16]

In recent years, several methods have been reported for the preparation of (*N*-isocyanimino)triphenylphosphorane ($CNNPPh_3$) **2** (Scheme 1).[17,18] There are several reports on the use of (*N*-isocyanimino)triphenylphosphorane **2** in the synthesis of metal complexes.[17,18] However, the 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,[19–21] we sought to develop a convenient preparation of 2-aryl-1,3,4-oxadiazoles **5a**–**g**. Herein, we report a hitherto unknown two-component reaction, which, starting from simple and readily available benzoic acid derivatives affords 2-aryl-1,3,4-oxadiazoles **5a**–**g** in a one-pot reaction with (*N*-isocyanimino)triphenylphosphorane **2** (Scheme 1).

2. Results and discussion

The benzoic acid derivative **1** and (*N*-isocyanimino)triphenylphosphorane **2** in dichloromethane react together in a 1:1 ratio at room temperature to produce 2-aryl-1,3,4-oxadiazoles **5** and triphenylphosphine oxide **6** (Scheme 1). The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed. The mechanism of the reaction between the benzoic acid derivative **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,[22] 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**.[23] Intramolecular aza-Wittig[23] reaction of iminophosphorane **4** would lead to the formation of 2-aryl-1,3,4-oxadiazoles **5** and triphenylphosphine **6** (Scheme 1). The structures of the products were deduced from their IR, ^1H NMR and ^{13}C NMR spectra. The mass spectra

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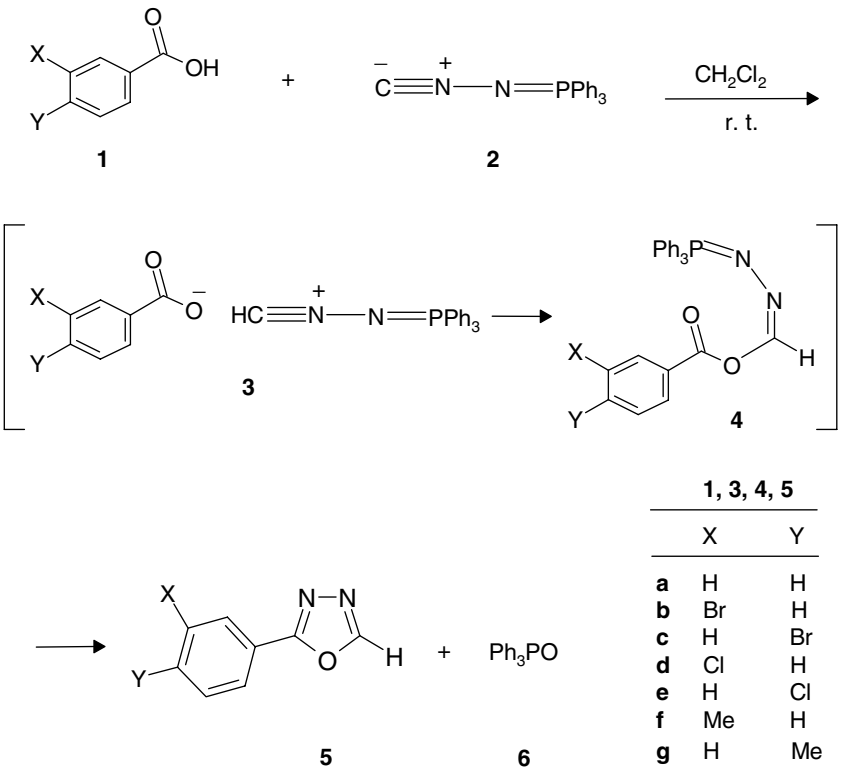

1, 3, 4, 5		
	X	Y
a	H	H
b	Br	H
c	H	Br
d	Cl	H
e	H	Cl
f	Me	H
g	H	Me

Scheme 1.

of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.

3. Conclusions

We believe that the reported method offers a mild, simple, and efficient route for the preparation of 2-aryl-1,3,4-oxadiazole derivatives. Its ease of work-up, high yields and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

4. General procedure

To a magnetically stirred solution of (*N*-isocyanimino)triphenylphosphorane[17] **2** (0.302 g, 1 mmol) in CH_2Cl_2 (8 ml) was added dropwise a solution of **1** (1 mmol) in CH_2Cl_2 (7 ml) over 15 min. The mixture was stirred for 12 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 (8:1)). The solvent was removed under reduced pressure and the products (**5a**–**g**) were obtained. The characterization data of the compounds are given below.

4.1. 2-Phenyl-1,3,4-oxadiazole 5a

White crystals; mp: 143.6 °C; Yield: 91%. IR (KBr) (ν_{max}, cm^{-1}): 3008, 1692, 1661, 1530, 723. ^1H NMR ($CDCl_3$, 250 MHz): δ_H 8.42 (s, 1H, oxadiazole); 8.11–8.05 (m, 2H, arom); 7.59–7.48 (m, 3H, arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 164.79 (1C, oxadiazole); 152.67 (1CH, oxadiazole); 132.03, 129.13, and 127.10 (5CH, arom), 123.42 (1C, arom). Anal. Calcd for $C_8H_6N_2O$ (146): C, 65.75; H, 4.14; N, 19.17. Found: C, 65.70; H, 4.39; N, 19.11. MS (EI) (*m*/*z*): 146 (M^+).

4.2. 2-(3-Bromophenyl)-1,3,4-oxadiazole 5b

White crystals; mp: 80.1 °C; Yield: 91%. IR (KBr) (ν_{max}, cm^{-1}): 3092, 2923, 1653, 1553, 1115, 730. ^1H NMR ($CDCl_3$, 250 MHz): δ_H 8.50 (s,1H, oxadiazole); 8.24–8.23 (m, 1H, arom); 8.04–8.01 (m, 1H, arom); 7.72–7.67 (m, 1H, arom); 7.44–7.34 (m, 1H, arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 163.53 (1C, oxadiazole); 152.87 (1CH, oxadiazole); 125.25 and 123.14 (2C, arom); 135.01, 130.73, 129.96, and 125.63 (4CH, arom). Anal. Calcd for $C_8H_5BrN_2O$ (225): C, 42.70; H, 2.24; N, 12.45. Found: C, 42.64; H, 2.29; N, 12.53. MS (EI) (*m*/*z*): 226 ($(M+2)^+$), 224 (M^+).

4.3. 2-(4-Bromophenyl)-1,3,4-oxadiazole 5c

White crystals; mp: 140.2 °C; Yield: 92%. IR (KBr) (ν_{max}, cm^{-1}): 3146, 3092, 2930, 1600, 1477, 1108, 831. ^1H NMR ($CDCl_3$, 250 MHz): δ_H 8.47 (s, 1H, oxadiazole); 7.98–7.87 (m, 2H, arom); 7.70–7.50 (m, 2H, arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 164.11 (1C, oxadiazole); 152.74 (1CH, oxadiazole), 126.82 and 122.35 (2C, arom), 131.83 and 128.51 (4CH, arom). Anal. Calcd for $C_8H_5BrN_2O$ (225): C, 42.70; H, 2.24; N, 12.45.

Found: C, 42.56; H, 2.17; N, 12.39. MS (EI) (*m*/*z*): 226 ($(M+2)^+$), 224 (M^+).

4.4. 2-(3-Chlorophenyl)-1,3,4-oxadiazole 5d

White crystals; mp: 115.3 °C; Yield: 86%. IR (KBr) (ν_{max}, cm^{-1}): 3031, 2923, 1554, 1123, 777. ^1H NMR ($CDCl_3$, 250 MHz): δ_H 8.50 (s, 1H, oxadiazole); 8.05–7.95 (m, 1H, arom); 7.86–7.78 (m, 1H, arom), 7.58–7.44 (m, 2H, arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 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). Anal. Calcd for $C_8H_5ClN_2O$ (180.5): C, 53.21; H, 2.79; N, 15.51. Found: C, 53.29; H, 2.85; N, 15.45. MS (EI) (*m*/*z*): 182 ($(M+2)^+$), 180 (M^+).

4.5. 2-(4-Chlorophenyl)-1,3,4-oxadiazole 5e

White crystals; mp: 127.1–128.4 °C; Yield: 83%. IR (KBr) (ν_{max}, cm^{-1}): 3077, 1608, 1485, 1092, 838, 738. ^1H NMR ($CDCl_3$, 250 MHz): δ_H 8.49 (s, 1H, oxadiazole); 8.03 (d, 2H, $^3J_{HH} = 8.4$ Hz, arom); 7.50 (d, 2H, $^3J_{HH} = 8.4$ Hz, arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 164.01 (1C, oxadiazole), 152.73 (1CH, oxadiazole), 138.36 and 121.92 (2C, arom); 129.55 and 128.38 (4CH, arom). Anal. Calcd for $C_8H_5ClN_2O$ (180.5): C, 53.21; H, 2.79; N, 15.51. Found: C, 53.15; H, 2.84; N, 15.46. MS (EI) (*m*/*z*): 182 ($(M+2)^+$), 180 (M^+).

4.6. 2-*m*-Tolyl-1,3,4-oxadiazole 5f

White crystals; mp: 64.4 °C; Yield: 92%. IR (KBr) (ν_{max}, cm^{-1}): 3108, 2985, 2408, 2277, 1554, 1500, 1115, 731. ^1H NMR ($CDCl_3$, 250 MHz): δ_H 8.46 (s, 1H, oxadiazole); 7.90–7.80 (m, 2H, arom); 7.43–7.31 (m, 2H, arom); 2.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 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). Anal. Calcd for $C_9H_8N_2O$ (160): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.42; H, 5.11; N, 17.43 . MS (EI) (*m*/*z*): 160 (M^+).

4.7. 2-*p*-Tolyl-1,3,4-oxadiazole 5g

White crystals; mp: 86.9 °C; Yield: 93%. IR (KBr) (ν_{max}, cm^{-1}): 3123, 2915, 1615, 1500, 1100, 954, 831, 738. ^1H NMR ($CDCl_3$, 250 MHz): δ_H 8.44 (s, 1H, oxadiazole), 7.99–7.83 (m, 2H, arom), 7.34–7.18 (m, 2H, arom), 2.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 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). Anal. Calcd for $C_9H_8N_2O$ (160): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.55; H, 5.09; N, 17.43. MS (EI) (*m*/*z*): 160 (M^+).

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