Turk J Chem
36 (2012) , 179 – 188.

doi:10.3906/kim-1102-3

One-pot synthesis of fully substituted 1,3,4-oxadiazole derivatives from aromatic carboxylic acids, cyclobutanone and *N*-isocyaniminotriphenylphosphorane

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Received: 03.02.2011

Reactions of *N*-isocyaniminotriphenylphosphorane with cyclobutanone in the presence of aromatic (or heteroaromatic) carboxylic acids proceeded smoothly at room temperature and in neutral conditions to afford sterically congested 1-(5-aryl-1,3,4-oxadiazol-2-yl)-1-cyclobutanol derivatives in high yields. The reaction proceeded smoothly and cleanly under mild conditions and no side reactions were observed. The structures of the products were deduced from their IR, ^{1}HNMR, and ^{13}CNMR spectra, and mass spectrometry.

Key Words: *N*-isocyaniminotriphenylphosphorane, intramolecular *aza*-Wittig reaction, 1,3,4-oxadiazole, aromatic carboxylic acid, cyclobutanone

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, compounds with

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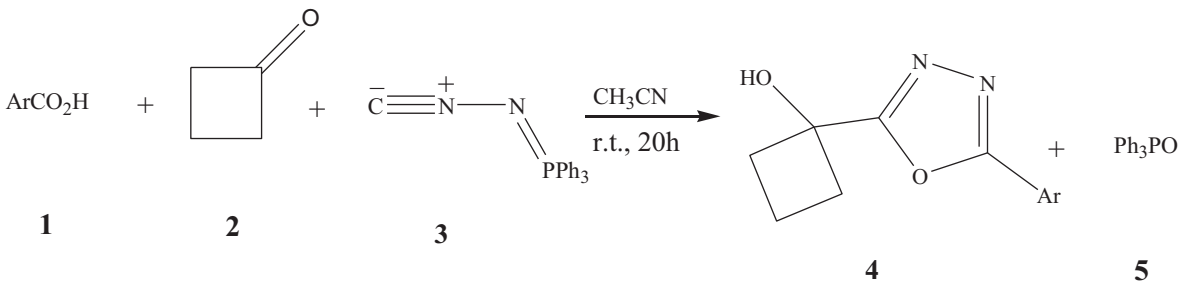
biological and pharmacological activity.[5–11] In the last years, several preparative procedures have been reported for the preparation and synthetic applications of iminophosphoranes.[5–13] The unique synthetic potential of iminophosphoranes results from the presence of electronrich nucleophilic nitrogen 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 iminophosphoranes' structures 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 its 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 on the use of *N*isocyaniminotriphenylphosphorane **3** in the preparation of metal complexes[12,13](Scheme 1). However, the role of *N*-isocyaniminotriphenylphosphorane **3** in organic chemistry remains almost unexplored.[12,13] The *N*-isocyaniminotriphenylphosphorane **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-(5-aryl-1,3,4-oxadiazol-2-yl)-1-cyclobutanols **4a-m** from *N*-isocyaniminotriphenylphosphorane **3** cyclobutanone **2** and aromatic (or heteroaromatic) carboxylic acids **1** in excellent yields under neutral conditions (Scheme 1).



Scheme 1. Synthesis of sterically congested 2,5-disubstituted 1,3,4-oxadiazoles derivatives from *N*-isocyaniminotriphenylphosphorane **3** cyclobutanone 2 and aromatic (or heteroaromatic) carboxylic acids **1**.

1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides.[32–34] They are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including antimicrobial, antifungal, anti-inflammatory, antihypertensive, analgesic, antibacterial, hypoglycemic, antimalarial, antitubercular and antidepressant.[32–34] Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multi-step 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*-isocyaniminotriphenylphosphorane **3**[24,31]

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 were TLC and NMR. TLC and NMR indicated that there was no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}CNMR 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 for the preparation of compounds 4

To a magnetically stirred solution of *N*-isocyaniminotriphenylphosphorane **3** (1 mmol) and cyclobutanone **2** (1 mmol) in CH_3CN (7 mL) was added dropwise of a solution of aromatic carboxylic acids **1** (1 mmol) in CH_3CN (5 mL) at room temperature over 15 min. The mixture was stirred for 20 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel powder; petroleum ether–ethyl acetate (3:1)). The solvent was removed under reduced pressure and the products were obtained. The characterization data of the compounds are given below:

1-(5-phenyl-1,3,4-oxadiazol-2-yl)cyclobutanol (4a)

Yellow oil (Yield: 85%). IR (neat): υ = 3276, 2992, 2949, 1548, 1451 and 783 cm^{-1} ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.95-2.05 (m, 2H, cyclobutane), 2.46-2.58 (m, 2H, cyclobutane), 2.72-2.81 (m, 2H, cyclobutane), 3.48 (s, 1H, OH), 7.41-8.08 (m, 5H, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.5 ($2CH_2$, cyclobutane) 71.2 (C, cyclobutane), 123.7 (C, arom) 127.0 (CH), 129.0 (CH), 131.9 (CH) 165.5 and 169.1 (2C, oxadiazole). Analysis of $C_{12}H_{12}N_2O_2$ (216.24). (% calculation/ found): C: 66.65/66.69, H: 5.59/5.64, N: 12.96/1291 MS, m/z(%): 216 (M^+, 18), 188 (35), 160 (100), 118 (50), 103 (47), 76 (73), 50 (23) and 42 (59).

1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4b)

Yellow oil (Yield: 85%). IR (neat): υ =3265, 2941, 1605, 1406, 1088, 843 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.93-2.08 ($2CH_2$, cyclobutane), 2.45-2.57 ($2CH_2$, cyclobutane), 2.72-2.82 ($2CH_2$, cyclobutane), 3.45 (s, 1H, OH), 7.49 (2d, 4H, J = 8.5 Hz, arom) and 7.99 (2d, 4H, J = 8.5 Hz, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.5 ($2CH_2$, cyclobutane), 71.1 (C, cyclobutane), 128.2 (CH), 129.4 (CH) 122.1 and 138.2 (2C, arom) 165.1 and 169.3 (2C, oxadiazole). Analysis of $C_{12}H_{11}ClN_2O_2$ (250.68). (% calculation/found): C: 57.49/5746, H: 4.42/4.46, N: 11.17/1120. MS, m/z(%): 250 (M^+, 55), 222 (48), 194 (100), 152 (39), 137 (62), 111 (30), 74 (29) and 42 (80).

1-[5-(4-ethylphenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4c)

Yellow crystals, (Yield 87%). Mp 77.2-78.3 °C IR (KBr): υ =3285, 2938, 1498, 1250, 1074, 838 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.26 (t, 3H, J = 7.5 Hz, CH_3 of Et), 1.92-2.0 ($2CH_2$, cyclobutane), 2.02-2.12

($2CH_2$, cyclobutane), 2.45-2.57 ($2CH_2$, cyclobutane), 2.71 (q, 2H, $J = 7.5$ Hz, CH_2 of Et), 2.43 (s, 3H, CH_3), 3.60 (s, 1H, OH), 7.31 and 7.96 (2d, 4H, $J = 7.5$ Hz, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.5 ($2CH_2$, cyclobutane) 15.2 (CH_3 of Et) 28.9 (CH_2 of Et), 71.1 (C, cyclobutane), 121.1 and 148.6 (2C, arom) 127.0 (CH), 128.5 (CH) 165.5 and 168.8 (2C, oxadiazole). Analysis of $C_{14}H_{16}N_2O_2$ (244.29), (% calculation/ found): C: 68.83/6878, H: 6.60/6.54, N: 11.47/11.51

1-[5-(3,5-dimethylphenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4d)

Yellow oil, (Yield: 86%). IR (neat): $v = 3212, 2949, 1560, 1429, 1043, 863$ cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.97-2.05 ($2CH_2$, cyclobutane), 2.46-2.63 ($2CH_2$, cyclobutane), 2.72-2.82 ($2CH_2$, cyclobutane), 2.38 (1s, 6H, $2CH_3$) 3.65 (1s, 1H, OH) 7.15 and 7.66 (2s, 3H, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.4 ($2CH_2$, cyclobutane) 21.2 (CH_3), 71.1 (C, cyclobutane) 123.4 and 138.8 (2C, arom) 124.7 (CH), 133.6 (CH), 165.8 and 170.0 (2C, oxadiazole). Analysis of $C_{14}H_{16}N_2O_2$ (244.29). (% calculation/ found): C: 68.83/68.86, H: 6.60/6.56, N: 11.47/11.43

1-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4e)

Yellow crystals, (Yield: 89%). Mp 127.2-128.7 °C. IR (KBr): v =3228, 2928, 1498, 1159, 1085, 823 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.92-2.06 ($2CH_2$, cyclobutane), 2.48-2.57 ($2CH_2$, cyclobutane), 2.72-2.82 ($2CH_2$, cyclobutane), 2.43 (s, 3H, CH_3) 3.60 (s, 1H, OH) 7.30 and 7.95 (2d, 4H, $J = 8$ Hz, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.5 ($2CH_2$, cyclobutane) 21.7 (CH_3) 71.2 (C, cyclobutane); 120.9 and 142.4 (2C, arom) 126.9 (CH), 129.7 (CH), 165.5 and 169.0 (2C, oxadiazole). Analysis of $C_{13}H_{14}N_2O_2$ (230.26). (% calculation/ found): C: 67.81/67.85, H: 6.13/6.17, N: 12.17/1214

1-[5-(2-Bromophenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4f)

Yellow oil (Yield: 87%). IR (neat): v =3284, 2939, 1523, 1454, 1094, 897, 754 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.92-2.2.05 ($2CH_2$, cyclobutane), 2.48-2.60 ($2CH_2$, cyclobutane), 2.72-2.83 ($2CH_2$, cyclobutane), 3.40 (s, 1H, OH) 7.36-7.49 (m, 2H, arom) 7.75 (d, $J = 7.75$ Hz, 1H, arom) 7.95 (d, $J = 7.5$ Hz, 1H, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.7 and 35.6 ($2CH_2$, cyclobutane) 71.3 (C, cyclobutane) 121.7 and 125.9 (2C, arom) 127.6 (CH), 131.8 (CH), 132.6 (CH), 134.5 (CH) 164.5 and 170.8 (2C, oxadiazole). Analysis of $C_{12}H_{11}BrN_2O_2$ (295.13). (% calculation/ found): C: 4884/4879, H: 376/373, N: 949/953.

4-[5-(1-hydroxycyclobutyl)-1,3,4-oxadiazol-2-yl]benzonitrile (4g)

Yellow oil, (Yield: 86%). IR (neat): v =3289, 2915, 2229, 1489, 1158, 1083, 854 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.91-2.10 ($2CH_2$, cyclobutane), 2.46-2.59 ($2CH_2$, cyclobutane), and 2.74-2.83 (3m, 6H, cyclobutane) 3.42 (s, 1H, OH) 7.82 and 8.20 (2d, 4H, $J = 8.5$ Hz, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.6 ($2CH_2$, cyclobutane) 71.2 (C, cyclobutane) 127.5 (CH), 132.9 (CH) 115.4 and 138.2 (2C, arom) 165.2 and 169.2 (2C, oxadiazole). Analysis of $C_{13}H_{11}N_3O_2$ (241.25). (% calculation/ found): C: 6472/6477, H: 460/456, N: 1742/1746.

1-[5-(4-Bromorophenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4h)

Yellow crystals, (Yield: 83%). Mp 117-118.9 °C. IR (KBr): v =3286, 2941, 1525, 1458, 1098, 891 cm^{-1} ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.87-2.05 ($2CH_2$, cyclobutane), 2.45-2.57 ($2CH_2$, cyclobutane), 2.75-2.78 ($2CH_2$, cyclobutane), 3.36 (s, 1H, OH), 7.64 and 7.91 (2d, 4H, J = 7.5 Hz, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.5 ($2CH_2$, cyclobutane), 71.2 (C, cyclobutane), 128.4 (CH), 132.4 (CH), 122.2 and 138.3 (2C, arom), 165.0 and 166.8 (2C, oxadiazole). Analysis of $C_{12}H_{11}BrN_2O_2$ (295.13). (% calculation/ found): C: 4884/4888, H: 376/3.80, N: 9.49/944.

1-[5-(3,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4i)

Yellow crystals, (Yield 84%). Mp 90.4-91.9 °C IR (KBr): v =3213, 2947, 1562, 1494, 1045, 827 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.84-2.04 ($2CH_2$, cyclobutane), 2.44-2.56 ($2CH_2$, cyclobutane), 2.73-2.78 ($2CH_2$, cyclobutane), 2.30 (s, 6H, $2CH_3$), 3.91 (s, 1H, OH), 7.19-7.78 (m, 3H, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.4 ($2CH_2$, cyclobutane), 19.6 and 19.9 ($2CH_3$) 71.0 (C, cyclobutane) 121.1, 137.5 and 141.1 (3C, arom), 124.5 (CH), 127.9 (CH), 129.2 (CH); 165.5 and 168.9 (2C, oxadiazole). Analysis of $C_{14}H_{16}N_2O_2$ (244.29). (% calculation/ found): C: 6883/6880, H: 6.60/665, N: 11.47/1144.

1-(5-(2-Thienyl)-1,3,4-oxadiazol-2-yl)cyclobutanol (4j)

Yellow oil (Yield: 81%). IR (neat): v = 3289, 2995, 2938, 1587, 1491 and 855 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.85-2.05 ($2CH_2$, cyclobutane), 2.44-2.56 ($2CH_2$, cyclobutane), 2.71-2.75 ($2CH_2$, cyclobutane), 3.62 (s, 1H, OH), 7.15-7.76 (m, 3H, arom. ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.4 ($2CH_2$, cyclobutane), 71.1 (C, cyclobutane), 124.9 (C, arom), 128.1 (CH), 130.0 (CH), 130.3 (CH) 164.5 and 168.5 (2C, oxadiazole). Analysis of $C_{10}H_{10}N_2O_2S$ (222.26). (% calculation/ found): C: 5404/5409, H: 4.53/4.50, N: 1260/1256.

1-[5-(2,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4k)

Yellow crystals (Yield 85%). Mp 82.2-83.7 °C IR (KBr): v =3215, 2951, 1564, 1495, 1059, 826 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.91-2.10 ($2CH_2$, cyclobutane), 2.43-2.54 ($2CH_2$, cyclobutane), 2.69-2.90 ($2CH_2$, cyclobutane), 2.37 and 2.65 (2s, 6H, $2CH_3$) 3.90 (s, 1H, OH) 7.09-7.92 (m, 3H, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.5 ($2CH_2$, cyclobutane), 21.4 and 21.9 ($2CH_3$), 71.1 (C, cyclobutane) 120.0, 138.3 and 141.7 (3C, arom) 126.9 (CH), 129.0 (CH), 132.5 (CH) 165.7 and 168.9 (2C, oxadiazole). Analysis of $C_{14}H_{16}N_2O_2$ (244.29). (% calculation/ found): C: 6883/6886, H: 6.60/664, N: 11.47/11.44.

1-[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4l)

Yellow oil, (Yield 82%). IR (neat): v =3230, 2925, 1489, 1155, 1089, 827 cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$) δ (ppm): 1.91-2.05 ($2CH_2$, cyclobutane), 2.45-2.58 ($2CH_2$, cyclobutane), 2.69-2.73 ($2CH_2$, cyclobutane), 2.67 (s, 3H, CH_3) 3.44 (s, 1H, OH) 7.18-8.00 (m, 4H, arom). ^{13}CNMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.8 and 35.5 ($3CH_2$, cyclobutane), 22.0 (CH_3), 71.1 (C, cyclobutane) 122.8 and 138.4 (2C, arom) 126.1 (CH), 129.0 (CH),

131.3 (CH), 131.7 (CH) 165.0 and 168.5 (2C, oxadiazole). Analysis of $C_{13}H_{14}N_2O_2$ (230.26). (% calculation/ found): C: 67.81/6777, H: 6.13/616, N: 1217/1213.

1-[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]cyclobutanol (4m)

Yellow oil, (Yield: 81%). IR (neat): v =3269, 2948, 1604, 1409, 1084, 847, 755 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.95-2.06 ($2CH_2$, cyclobutane), 2.46-2.55 ($2CH_2$, cyclobutane), 2.72-2.77 ($2CH_2$, cyclobutane), 3.87 (s, 1H, OH), 7.29-8.00 (m, 4H, arom). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.6 and 35.6 ($2CH_2$, cyclobutane), 71.2 (C, cyclobutane), 121.8 and 126.2 (2C, arom), 127.7 (CH), 131.3 (CH), 132.5 (CH), 134.4 (CH), 165.0 and 168.9 (2C, oxadiazole). Analysis of $C_{12}H_{11}ClN_2O_2$ (250.68). (% calculation/ found): C: 57.49/57.54, H: 4.42/4.38, N: 11.17/11.20.

Results and discussion

In recent years, several synthetic methods have been reported for the preparation of *N*-isocyaniminotriphenylphosphorane ($CNNPPh_3$) **3** (Scheme 1).[12,13] There are several reports on the use of *N*-isocyaniminotriphenylphosphorane **3** in the synthesis of metal complexes.[12,13] However, application of **3** in the synthesis of organic compounds has been fairly rare.[23−28] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[23−31] we sought to develop a convenient preparation of 1-(5-aryl-1,3,4-oxadiazol-2-yl)-1-cyclobutanols **4** from aromatic (or heteroaromatic) carboxylic acids **1** and *N*-isocyaniminotriphenylphosphorane **3** in excellent yields under neutral conditions (Scheme 1).

The carboxylic acid derivative **1** with cyclobutanone **2** and *N*- isocyaniminotriphenylphosphorane **3** in CH_3CN react together in a 1:1:1 ratio at room temperature to produce sterically congested 2,5-disubstituted 1,3,4-oxadiazoles **4** and triphenylphosphine oxide **5** (Scheme 1 and Table). The reaction proceeds smoothly and cleanly under mild conditions. The suggested mechanism for this reaction is provided 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*-isocyaniminotriphenylphosphorane **3** to cyclobutanone **2**, which facilitates by 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 an 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** (Scheme 2). The structures of the products **4a-m** were deduced from their IR, ^{1}HNMR, and ^{13}CNMR spectra. For example the IR spectrum of **4a** showed strong absorptions at 3276 (OH), 2992 (CH), 1548 (C=C, aromatic) 1451 (C=C, aromatic) and 783 (aromatic) cm^{-1}. The ^{1}HNMR spectrum of **4a** exhibited 3 multiplets for the cyclobutane (δ = 1.95-2.05, 2.46-2.58 and 2.72-2.81 ppm), a singlet for OH (δ = 3.48 ppm), and a multiplet for H-Ar (7.41-8.08 ppm). The ^{1}H decoupled ^{13}CNMR spectrum of **4a** showed 9 distinct resonances [δ = 12.8 and 35.5 (2 CH_2, cyclobutane); 71.2 (1 C, cyclobutane); 123.7 (1 C, arom.); 127.0, 129.0 and 131.9 (3 CH, arom.); 165.5 and 169.1 (2 C, oxadiazole)] that are in agreement with the formula and structure of **4a**. Partial assignment of these resonances is given in the spectral analysis section (see Experimental section). The ^{1}H and ^{13}CNMR spectra of compounds **4bm** were similar to those of **4a**, except for the aromatic or heteroaromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

Table. Synthesis of disubstituted 1,3,4-oxadiazole derivatives **4** (see Scheme 1).

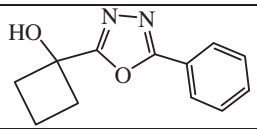
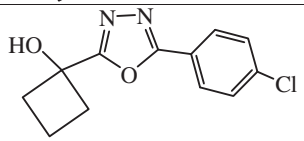
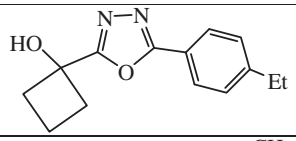
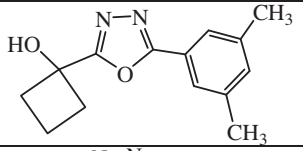
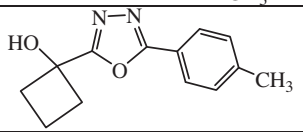
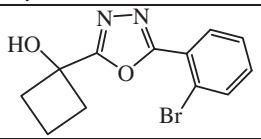
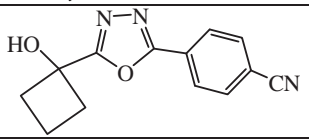
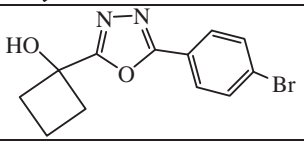
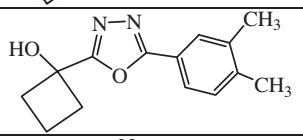
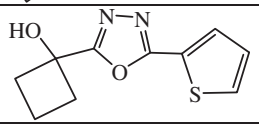
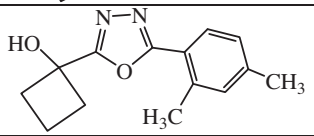
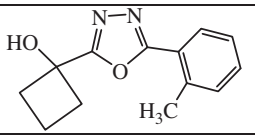
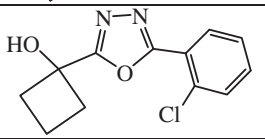
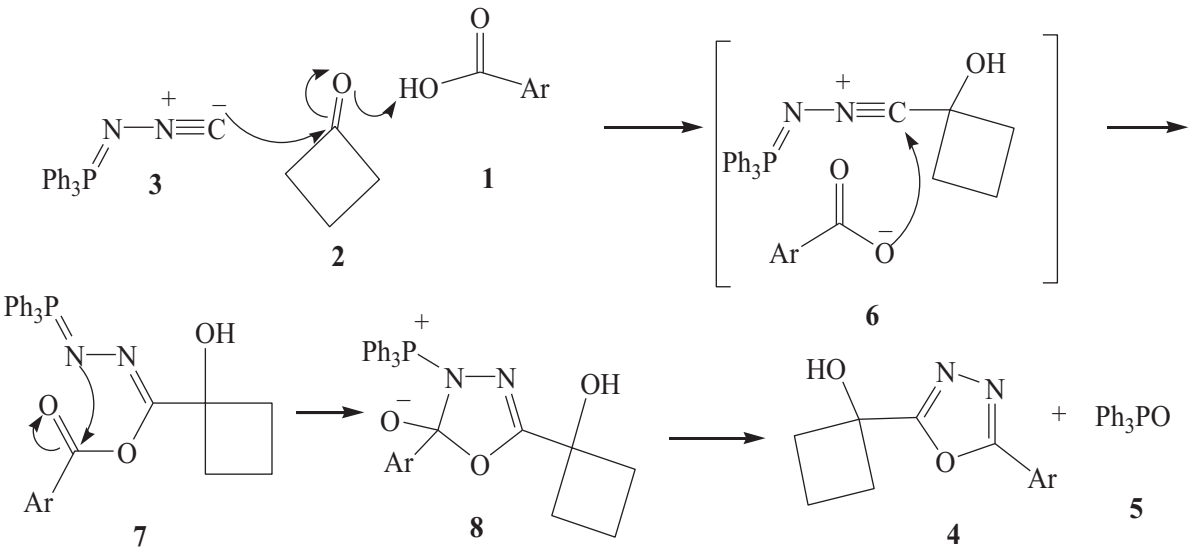
4	Ar	Product	Yield (%)[a]
a	C_6H_5		85
b	4-ClC_6H_4		85
c	4-EtC_6H_4		87
d	3,5-diMeC_6H_4		86
e	4-MeC_6H_4		9
f	2-BrC_6H_4		87
g	4-CNC_6H_4		86
h	4-BrC_6H_4		83
i	3,4-diMeC_6H_4		84
j	C_4H_3S		81
k	2,4-diMeC_6H_4		85

Table. Continued.

4	Ar	Product	Yield (%)[a]
l	2-MeC_6H_4		82
m	2-ClC_6H_4		81

[a]Yield of isolated **4**.



Scheme 2. Proposed mechanism for the formation of disubstituted 1,3,4-oxadiazole derivatives **4**.

In summary, we have found a new method for the preparation of sterically congested 2,5-disubstituted 1,3,4-oxadiazole derivatives **4** from aromatic (or heteroaromatic) carboxylic acids **1**, cyclobutanone **2** and *N*-isocyaniminotriphenylphosphorane **3** in excellent yields under neutral conditions. We think 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.

Conclusions

We think that the reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazole derivatives, by a sequence of multicomponent reactions and an intramolecular *aza*-Wittig closure. Due to the easy availability of the synthetic approach and the neutral ring closure conditions, this

new synthetic approach discussed here has potential in synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles, which are of considerable interest as potential biologically active compounds or pharmaceuticals.

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