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Isocyanide-based three-component reactions: synthesis of some novel 1,3,4-oxadiazole derivatives from *N*-isocyaniminotriphenyl phosphorane, aromatic aldehydes and aromatic carboxylic acids

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ABSTRACT

A wide variety of disubstituted oxadiazole derivatives have been synthesized *via* a one-pot three-component reaction of *N*-isocyaniminotriphenylphosphorane, an aromatic aldehyde, and aromatic carboxylic acid in CH_3CN at ambient temperature in high yields without using any catalyst or activation. The procedure provides an alternative method for the synthesis of fully substituted oxadiazole derivatives.

KEYWORDS

Oxadiazole derivatives;
N-isocyaniminotriphenyl phosphorane;
Aza-wittig-type reaction;
Aromatic aldehydes;
Aromatic carboxylic acid.

INTRODUCTION

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, and several interesting heterocyclization reactions involving iminophosphoranes have been reviewed[1-7]. These compounds can easily be converted through *aza*-Wittig reaction with isocyanates, carbon dioxide, or carbon disulfide into functionalized heterocumulenes which exhibit a rich chemistry of unusual synthetic promise[1-7]. The nucleophilicity at the nitrogen is a factor of essential mechanistic importance in the use of these iminophosphoranes as *aza*-Wittig reagents. In recent years, several methods have been reported for the use of *N*-isocyaniminotriphenylphosphorane in the preparation of metal complexes[8, 9]. However, the role of *N*-isocyaniminotriphenylphosphorane in organic chemistry remains almost unexplored. The *N*-isocyaniminotriphenylphosphorane 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[10]. In the present study, we wish to report the synthesis of some new 2,5-disubstituted 1,3,4-oxadiazole derivatives *via* a one-pot three-component reaction between *N*-isocyaniminotriphenyl phosphorane, benzaldehyde

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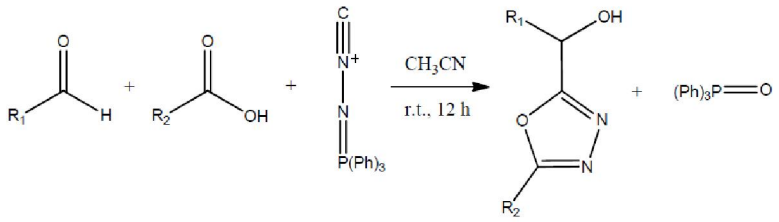

1 2 3 4a-j 5

R_1 and R_2 = Aryl

Scheme 1 : Synthesis of 1,3,4-oxadiazole derivatives 4a-j from aldehyde derivative 1 and aromatic carboxylic acid 2 and *N*-isocyaniminotriphenylphosphorane 3

derivatives and various carboxylic acids in CH_3CN at ambient temperature in high yields (Scheme 1).

EXPERIMENTAL

N-isocyaniminotriphenylphosphorane 3 was prepared based on reported procedures[8, 9]. Starting materials and solvents were obtained from Merck (Darmstadt, Buchs, Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions were TLC and NMR. Melting points were measured with an Electrothermal 9100 apparatus (LABEQUIP LTD., Markham, Ontario, Canada) and are uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer (JASCO Ltd., Easton, MD). ^1H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-250 Avance spectrometer (Bruker Ltd., Ettlingen, Germany) at 250.0 and 62.5 MHz, respectively. The TLC plates were prepared from Merck silica gel powder.

General procedure for the preparation of compounds 4a-j

A mixture of *N*-isocyaniminotriphenyl phosphorane (2.0 mmol), benzaldehyde derivatives (2.0 mmol), and aromatic carboxylic acid (2.0 mmol) in 5 mL CH_3CN was stirred for the time specified in TABLE 1 at room temperature. The solvent was removed under reduced pressure and the products were purified by preparative layer chromatography (PLC) [silica gel (HF_{254}) powder; petroleum ether/ethyl acetate 3:1].

The characterization data of the compounds are given below

4-[5-hydroxy(phenyl)]methyl-1,3,4-oxadiazol-2-yl]phenol (4a:

White crystals; Yield 78%; m.p.: 145.5-147.1 °C; ^1H NMR ($CDCl_3$, 250 MHz): δ_H 2.397 (s, 3H, CH_3), 4.128 (s, 1H, OH, exchanged by D_2O addition), 6.135 (s, H, CH aliphatic), 7.23-7.97(9H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 21.64(CH_3), 68.40 (*C*-OH), 126.62, 127, 128.88, 128.94 and 129.7 (9CH, arom), 121.57, 137.91 and 142.54 (3C,arom), 163.35 and 165.25 (2 C=N of oxadiazol).

4-chlorophenyl-5(3-methylephenyl)-1,3,4-oxadiazol-2-yl-methanol (4b)

White crystals; Yield 90 %; m.p.: 185.5-187.1 °C; ^1H NMR ($CDCl_3$, 250 MHz): δ_H 2.407 (s, 3H, CH_3), 3.721 (s, 1H, OH, exchanged by D_2O addition), 6.114 (s, H, CH aliphatic), 7.056-7.898 (8H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 21.30 (CH_3), 67.77 (*C*-OH), 124.19, 127.51, 127.99, 128.97, 129.12 (8CH, arom), 132.93, 134.94, and 139.00 (3C, arom), 156.42 and 163.34 (2 C=N of oxadiazol).

4-cholorophenyl-5-(3,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl methanol (4c)

White crystals; Yield 87 %; m.p.: 150.5-152.5 °C; IR (KBr) (υ_{max}, cm^{-1}): 3417 (OH), 1614 (C=N), 1593-1403 (C=C of arom); ^1H NMR ($CDCl_3$, 250 MHz): δ_H 2.044 and 2.287(s, 6H, 2 CH_3), 5.554 (s, 1H, OH, exchanged by D_2O addition), 6.156 (s, H, CH aliphatic), 7.194-7.910 (7H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 19.67 and 20.00 ($2CH_3$), 66.79 (*C*-OH), 120.61, 124.55, 127.94, 129.55, 130.13, 130.28, 130.96 (7CH, arom),

112.86, 137.64, 132.25 and 141.56 (5C, arom), 159.98 and 165.82 (2 C=N of oxadiazol).

3-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl(hydroxyl)methyl]benzonitril (4d)

White crystals; Yield 79 %; m.p.: 150.5-152.5 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 4.235 (s, 1H, OH, exchanged by D_2O addition), 6.352 (s, H, CH aliphatic), 7.536-8.259 (7H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 19.66 and 20.00 ($2CH_3$), 67.21 (*C*-OH), 129.78, 130.13, 130.91, 132.52 (8CH, arom), 113.14, 128.43 and 139.03 (4C, arom), 162.51 and 164.02 (2 C=N of oxadiazol).

3-hydroxy[5-(3-methyl phenyl)-1,3,4 oxadiazol-2-yl]methyle benzonitril (4e)

White crystals; Yield 85 %; m.p.: 148.5-150.1 °C; IR (KBr) ($_{max}$, cm^{-1}): 3030 (OH), 1703 (C=N), 1563-1454 (C=C of arom). ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 2.418 (s, 3H, CH_3), 3.555 (s, 1H, OH, exchanged by D_2O addition), 6.187 (s, H, CH aliphatic), 7.263-7.915 (8H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 21.29 (CH_3), 68.90 (COH), 124.22, 127.52, 129.03, 129.71, 130.15, 130.94 (8CH, arom)1 32.53, 133.10, and 139.25 (4C, arom), 159.98 and 162.82 (2 C=N of oxadiazol).

3-[5-(3,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl(hydroxyl)methyl]phenyl cyanide (4f):

White crystals; Yield 85 %; m.p.: 155.5-157.1 °C; IR (KBr) ($_{max}$, cm^{-1}): 3445 (OH), 1616 (C=N), 1558-1448 (C=C of arom). ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 2.044 and 2.287 (s, 6H, $2CH_3$), 5.554 (s, 1H, OH, exchanged by D_2O addition), 6.156 (s, H, CH aliphatic), 7.194-7.910 (7H,m,CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 19.67,20 ($2CH_3$), 66.79 (COH) 120.61, 124.55, 127.94, 129.55, 130.13, 130.28, 130.96 (7CH, arom) 112.86, 132.25, 137.64, and 141.56 (5C, arom), 161.01 and 165.87 (2 C=N of oxadiazol).

3-hydroxy(5-phenyl-1,3,4-oxadiazol-2yl) methyl phenyl cyanide (4g)

White crystals; Yield 79 %; m.p.: 175.5-178.1 °C; IR (KBr) ($_{max}$, cm^{-1}): 3030 (OH), 1703 (C=N), 1563-1454 (C=C of arom). ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 3.970 (s, 1H, OH, exchanged by D_2O addition), 6.202 (s, H, CH aliphatic), 7.264-8.018 (9H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 67.22 (C-OH), 113.12 (C-CN), 123.34 (Ca"N) 127.06, 129.12, 129.70, 130.14, 130.91, 132.23, 132.51 (9 CH, arom) 113.09, and 139.33 (3C, arom), 159.98 and 162.82 (2 C=N of oxadiazol).

4-cholorophenyl-5-phenyl-1,3,4-oxadiazol-2-yl methanol (4h)

White crystals; Yield 81 %; m.p.: 180.5-182,5 °C; IR (KBr) ($_{max}$, cm^{-1}): 3418 (OH), 1652 (C=N), 1552-1409 (C=C of arom). ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 3.922 (s, 1H, OH, exchanged by D_2O addition), 6.122 (s, H, CH aliphatic), 7.098-8.110 (9H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 67.76 (C-OH), 113.12 (C-CN), 123.34 (Ca"N) 127.04, 127.99, 128.69, 129.10, 129.94 (9 CH, arom) 132.087, 134.94 and 136.223 (3C, arom), 153.18 and 163.82 (2 C=N of oxadiazol).

4-choloropheny-5-(cholorophenyl)-1,3,4-oxadiazol-2-yl methanol (4i)

White crystals; Yield 82 %; m.p.: 175.5-178.1 °C; IR (KBr) ($_{max}$, cm^{-1}): 3030 (OH), 1703 (C=N), 1563-1454 (C=C of arom). ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 3.494 (s, 1H, OH, exchanged by D_2O addition), 6.122 (s, H, CH aliphatic), 7.262-8.184 (8H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 67.32 (COH), 113.12 (CCN), 123.34 (Ca"N) 127.95, 128.30, 129.19, 129.500 (8CH, arom) 142.07, 139.35, 136.7 and 147.12 (4C, arom), 150.18 and 164.093 (2 C=N of oxadiazol).

3-cholorophenyl-5-(3-methylephenyl)1,3,4-oxadiazol-2-yl methanol (4j)

White crystals; Yield 85 %; m.p.: 145.5-147.1 °C; IR (KBr) ($_{max}$, cm^{-1}): 3030 (OH), 1703 (C=N), 1563-1454 (C=C of arom). ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 3.494 (s, 1H, CH_3), 4.141 (s, 1H, OH, exchanged by D_2O addition), 6.147 (s, H, CH aliphatic), 7.024-7.910 (8H, m, CH arom). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 21.26 (CH_3), 67.67 (COH), 113.86, 115.74, 116.08, 122.13, 123.13, 124.21, 127.52, 128.67 (8CH, arom) 1132.89, 138.98, 140.15 and 140.26 (4C, arom), 161.02 and 164.95 (2 C=N of oxadiazol).

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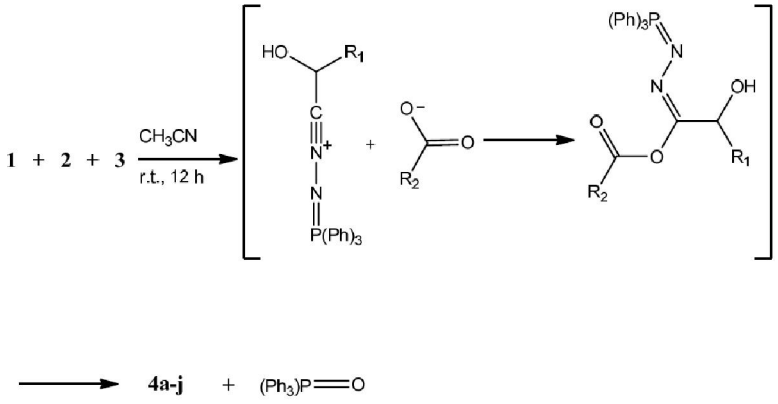
TABLE 1 : Synthesis of 1,3,4- oxadiazole derivatives 4a-j from aldehyde derivative 1 and aromatic carboxylic acid 2 in the presence of *N*-isocyaniminotriphenylphosphorane 3 in 5 mL CH_3CN at room temperature

Entry	Products	R_1	R_2	Reaction time (h)	Yield (%)[a]
1	4-a	C_6H_5	4-CH_3-C_6H_4	12	78
2	4-b	4-Cl-C_6H_4	3-CH_3-C_6H_4	11	90
3	4-c	4-Cl-C_6H_4	3,4-CH_3-C_6H_3	11	87
4	4-d	3-CN- C_6H_4	4-Br- C_6H_4	11	79
5	4-e	3-CN- C_6H_4	3-CH_3-C_6H_4	11	85
6	4-f	3-CN- C_6H_4	3,4-CH_3-C_6H_3	12	85
7	4-g	3-CN- C_6H_4	C_6H_5	11	79
8	4-h	4-Cl-C_6H_4	C_6H_5	11	81
9	4-i	4-Cl-C_6H_4	4-Cl-C_6H_4	11	82
10	4-j	3-Cl-C_6H_4	3-CH_3-C_6H_4	11	85

[a] **Isolated yield**



Scheme 2 : Proposed mechanism for the formation of 4a-j

RESULTS AND DISCUSSION

As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds[11–21], we have synthesized new disubstituted 1,3,4-oxadiazole derivatives 4 (4a-j, TABLE 1) *via* a one-pot three component reaction between benzaldehyde derivative 1, acarboxylic acid 2 and *N*-isocyaniminotriphenylphosphorane 3 (1:1:1 ratio) at room temperature in good to excellent yields of products (See TABLE 1). The reaction proceeds smoothly and cleanly under mild conditions and no side reaction was observed. The pure products are stable at room temperature for several months.

The structures of the products were deduced from their IR, ^1H and ^{13}C NMR spectra. A reasonable mechanism for the formation of compounds 4a-j is shown in Scheme 2.

CONCLUSION

In conclusion, we are reporting here "One-pot" synthesis of new 1,3,4-oxadiazole derivatives *via* a three-component reaction between *N*-isocyaniminotriphenylphosphorane, benzaldehyde derivatives and various carboxylic acids in CH_3CN at ambient temperature for 12 hrs in high yields.

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