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A Simple, Practical and Efficient Method for the Synthesis of New Disubstituted 1,3,4-oxadiazoles

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Abstract

Reactions of *N*-isocyaniminotriphenylphosphorane with α- chloroketones in the presence of aromatic carboxylic acids proceed smoothly at room temperature and in neutral conditions to afford new disubstituted 1,3,4-oxadiazole derivatives in high yields.

Keywords: *N*-isocyaniminotriphenylphosphorane, aromatic carboxylic acid, α- chloroketone, 1,3,4-oxadiazole, aza-Wittig reaction

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Introduction

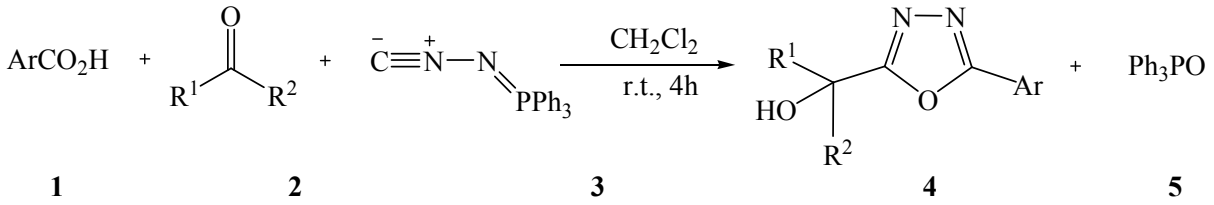
Organophosphorus compounds have been extensively employed in organic synthesis as useful reagents, as well as ligands, in a number of transition metal catalysts [1]. Iminophosphoranes are a class of special type of zwitterions, which bear a strongly nucleophilic electron rich nitrogen. The electron distribution around the P^{+}–N^{-} bond and its consequent chemical implications have been probed and assessed through theoretical, spectroscopic and crystallographic investigations [2]. The proton affinity of these iminophosphoranes can be used as a molecular guide to assess their utility as synthetic reagents [2] and their function as ligands in coordination and organometallic chemistry [1c, 2].

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 heterocyclic compounds. Several interesting heterocyclization reactions involving iminophosphoranes have been reviewed [2]. 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 [2].

The nucleophilicity at the nitrogen is a factor of essential mechanistic importance in the use of these iminophosphoranes as *aza*-Wittig reagents [2]. Iminophosphoranes (phosphazenes) are very important reagents in synthetic organic chemistry, especially in C-C and C-N bonds formation; synthesis of naturally occurring products, compounds with biological and pharmacological activity [2-5]. According to the presence of two functional groups in *N*-isocyaniminotriphenylphosphorane **3**, this reagent can plays new and effective role in multicomponent reactions[5] for the preparation of heterocyclic comounds [6]. There are several reports on the use of **3** in the synthesis of metal complexes [7]. *N*-isocyaniminotriphenylphosphorane **3** is expected to have synthetic potential because it makes a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality [6,7]. In continuation of our interest in the synthesis of organophosphorus compounds [8], we studied the synthetic chemistry of the *N*-isocyaniminotriphenylphosphorane **3** [6].

In recent years there has been considerable investigation on different classes of oxadiazoles. In particular, compounds containing 1,3,4-oxadiazole nucleus have been shown to possess a wide range of pharmacological and therapeutic activities. They have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides. Some 2,5-

disubstituted 1,3,4-oxadiazole derivatives have exhibited analgesic, anti-inflammatory, anticonvulsant, tranquilizing, myorelaxant, antidepressant, vasodilatatory, diuretic, antiulcer, antiarythmic, antiserotoninic, spasmolytic, hypotensive, antibronchocontrictive, anticholinergic, and antiemetic activities. Furthermore, many 2,5-disubstituted 1,3,4-oxadiazole derivatives have been reported as active inhibitors of several enzymes. [9]. Several methods have been reported for the synthesis of 1,3,4-oxadiazoles. These protocols are multi-step in nature [10]. As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds [11], we sought to develop a convenient preparation of disubstituted 1,3,4-oxadiazole derivatives **4a-h**. Herein we report a simple, practical one-pot three-component reaction which starting from readily available *α*-chloroketones **2** affords disubstituted 1,3,4-oxadiazole derivatives **4a-h** (Scheme 1 and Table 1).



Scheme 1. Three-component synthesis of disubstituted 1,3,4-oxadiazole derivatives **4** (See **Table 1**).

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

Entry	Ar	R^1	R^2	%Yield[a,b]
4a	4-BrC_6H_4	CH_2Cl	CH_2Cl	88
4b	3-MeC_6H_4	CH_2Cl	CH_2Cl	91
4c	4-BrC_6H_4	CH_3	$CHCl_2$	82
4d	3,4-diMeC_6H_3	CH_3	$CHCl_2$	86
4e	3-MeC_6H_4	CH_3	$CHCl_2$	80
4f	4-BrC_6H_4	CH_3	CH_2Cl	90
4g	3,4-diMeC_6H_3	CH_3	CH_2Cl	91
4h	3-MeC_6H_4	CH_3	CH_2Cl	93

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 and are uncorrected. IR spectra were measured on a Jasco FT-IR 6300 spectrometer. ^{1}H and ^{13}C NMR 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. The results agreed favorably with the calculated values.

Preparation of N-isocyaniminotriphenylposphorane **3**

CH_2Cl_2 (60 mL), PPh_3 (15.74 g, 0.06 mol), NEt_3 (freshly distilled from KOH; 5.06 g, 0.05 mol) and formylhydrazine (dried in high-vacuum at 45 °C; 1.53 g, 0.025 mol) were placed in a reaction flask. The slurry was then heated to 50–60 °C, and CCl_4 (7.70 g, 0.05 mol) was added dropwise over a period of about 30 min. The mixture was kept at 50–60 °C for at least 5–6 h. After cooling to room temperature, 25 mL of a saturated aqueous Na_2CO_3 solution was added, the layers were separated, and the aqueous layer was washed with two 5-mL portions of CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered. After evaporation of the solvent, the residue was dried under vacuum, pulverised, stirred in 20 mL of ethanol/water (1:1.5) and collected on a frit. Recrystallisation from hot ethanol yielded 3.02 g (40%) of an orange-brown crystalline material (m.p. 159–160 °C, dec.) [7].

General procedure for the preparation of compounds 4a-h; general procedure exemplified for **4a**

To a magnetically stirred solution of *N*-isocyaniminotriphenylphosphorane (1 mmol, 0.302 g) and 1,3-dichloroacetone (1 mmol, 0.127 g) in CH_2Cl_2 (7 ml) was added dropwise of a solution of 4-bromobenzoic acid (1 mmol, 0.201 g) in CH_2Cl_2 (5 ml) at room temperature over 15 min. The mixture was stirred for 4 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel; petroleum ether–ethyl acetate (2:1)). The solvent was removed under reduced pressure and the products were obtained. The characterization data of the compounds are given below:

2-(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-1,3-dichloropropan-2-ol **(4a)**

White crystals; mp: 158.0-160.6 °C; Yield: 88%. IR (KBr) (υ_{max}, cm^{-1}): 3103 (br), 1602, 1484, 1125. Anal.Calcd for $C_{11}H_9BrCl_2N_2O_2$ (352.01): C, 37.53; H, 2.58; N, 7.96 %. Found: C, 37.49; H, 2.65; N, 7.93%. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 3.66 (1 s, OH, exchanged by D_2O addition), 4.13 (1 s, 4 H, $2CH_2Cl$), 7.67 and 7.94 (d, $^3J_{HH}$ = 8.12 Hz, 4H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 47.09 ($2CH_2Cl$), 73.36 (C aliphatic), 122.11 and 127.09 (2C, arom), 128.50 and 132.52 (4 CH, arom), 164.67 and 165.15 (2 C=N).

1,3-dichloro-2-(5-m-tolyl-1,3,4-oxadiazol-2-yl)propan-2-ol **(4b)**

White crystals; mp: 100-102 °C; Yield: 91%. IR (KBr) (υ_{max}, cm^{-1}): 3136 (br), 1602, 1550, 1088. Anal.Calcd for $C_{12}H_{12}Cl_2N_2O_2$ (287.14): C, 50.19; H, 4.21; N, 9.76 %. Found: C, 50.23; H, 4.26; N, 9.80 %. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 2.44 (s, 3H, CH_3), 3.65 (1 s, OH, exchanged by D_2O addition), 4.14 (1 s, 4 H, 2 CH_2Cl), 7.39-7.89 (m, 4H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 21.13 (CH_3), 47.13 ($2CH_2Cl$), 74.67 (C aliphatic), 122.12 and 126.90 (2C, arom), 124.70, 127.64, 128.53 and 133.09 (4 CH, arom), 166.02 and 167.01 (2 C=N).

2-(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-1,1-dichloropropan-2-ol **(4c)**

White crystals; mp: 138.5-140.0 °C; Yield: 82%. IR (KBr) (υ_{max}, cm^{-1}): 3232 (br), 1595, 1082. Anal.Calcd for $C_{11}H_9BrCl_2N_2O_2$ (352.01): C, 37.53; H, 2.58; N, 7.96 %. Found: C, 37.48; H, 2.65; N, 7.90 %. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 1.95 (s, 3H, CH_3), 3.75 (s, OH, exchanged by D_2O addition), 6.08 (1 s, 2H, $CHCl_2$), 7.66 and 7.92 (d, $^3J_{HH}$ = 7 Hz, 4H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 22.41 (CH_3), 75.40 (C aliphatic), 86.34 ($CHCl_2$), 122.13 and 127.15 (2C, arom), 128.50 and 132.52 (4 CH, arom), 165.68 and 166.24 (2 C=N).

1,1-dichloro-2-(5-(3,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol **(4d)**

White crystals; mp: 85.4-86.5 °C; Yield: 86%. IR (KBr) (υ_{max}, cm^{-1}): 3262 (br), 1683, 1491, 1100. Anal.Calcd for $C_{13}H_{14}Cl_2N_2O_2$ (301.17): C, 51.84; H, 4.69; N, 9.30 %. Found: C, 51.90; H, 4.76; N, 9.26 %. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 1.95 and 2.33 (2s, 9H, $3CH_3$), 3.75 (s, OH, exchanged by D_2O addition), 6.11 (1 s, 2H, $CHCl_2$), 7.24 and 7.82 (m, 3H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 19.71, 20.04 and 22.25 ($3CH_3$), 75.33 (C aliphatic), 86.30 ($CHCl_2$), 120.64, 137.70 and 141.64 (3C, arom), 124.64, 128.04 and 130.34 (3CH, arom), 165.78 and 165.94 (2 C=N).

1,1-dichloro-2-(5-m-tolyl-1,3,4-oxadiazol-2-yl)propan-2-ol **(4e)**

White crystals; mp: 119.2-121.4 °C; Yield: 80%. IR (KBr) (υ_{max}, cm^{-1}): 3265 (br), 1561, 1089. Anal.Calcd for $C_{12}H_{12}Cl_2N_2O_2$ (287.14): C, 50.19; H, 4.2; N, 9.76 %. Found: C, 50.23; H, 4.16; N, 9.80 %. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 1.96 and 2.56 (2s, 6H, $2CH_3$), 3.86 (s, OH, exchanged by D_2O addition), 6.10 (1 s, 2H, $CHCl_2$), 7.38 - 7.88 (m, 4H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 21.33 and 22.33 ($2CH_3$), 75.34 (C aliphatic), 86.80 ($CHCl_2$), 123.80 and 139.09 (2C, arom), 124.28, 127.60, 129.05 and 133.03 (4CH, arom), 165.70 and 165.94 (2 C=N).

2-(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-1-chloropropan-2-ol **(4f)**

White crystals; mp: 108.0-109.2 °C; Yield: 90%. IR (KBr) (υ_{max}, cm^{-1}): 3203 (br), 1602, 1067. Anal.Calcd for $C_{11}H_{10}BrCl_2N_2O_2$ (317.57): C, 41.60; H, 3.17; N, 8.82 %. Found: C, 41.54; H, 3.22; N, 8.85 %. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 1.82 (s, 3H, CH_3), 3.76 (s, OH, exchanged by D_2O addition), 3.90 and 4.03 (AB-quartet, $^2J_{HH}$ = 11.37 Hz, 2H, CH_2Cl), 7.65 and 7.91 (d, $^3J_{HH}$ = 8.5 Hz, 4H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 24.61 (CH_3), 51.64 (C aliphatic), 71.13 (CH_2Cl), 122.27 and 126.85 (2C, arom), 128.44 and 132.46 (4 CH, arom), 163.05 and 164.72 (2 C=N).

1-chloro-2-(5-(3,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol **(4g)**

White crystals; mp: 115.5-116.5 °C; Yield: 91%. IR (KBr) (υ_{max}, cm^{-1}): 3303 (br), 1558, 1097. Anal.Calcd for $C_{13}H_{15}ClN_2O_2$ (266.72): C, 58.54; H, 5.67; N, 10.50 %. Found: C, 58.61; H, 5.70; N, 10.45 %. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 1.79, 2.31 and 2.34 (3s, 9H, $3CH_3$), 3.76 (s, OH, exchanged by D_2O addition), 3.90 and 4.03 (AB-quartet, $^2J_{HH}$ = 11.25 Hz, 2H, CH_2Cl), 7.24-7.91 (m, 3H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 19.68, 20.0 and 24.58 ($3CH_3$), 51.77 (C aliphatic), 71.05 (CH_2Cl), 120.90, 137.61 and 141.38 (2C, arom), 124.55, 128.38 and 130.29 (3 CH, arom), 165.70 and 167.23 (2 C=N).

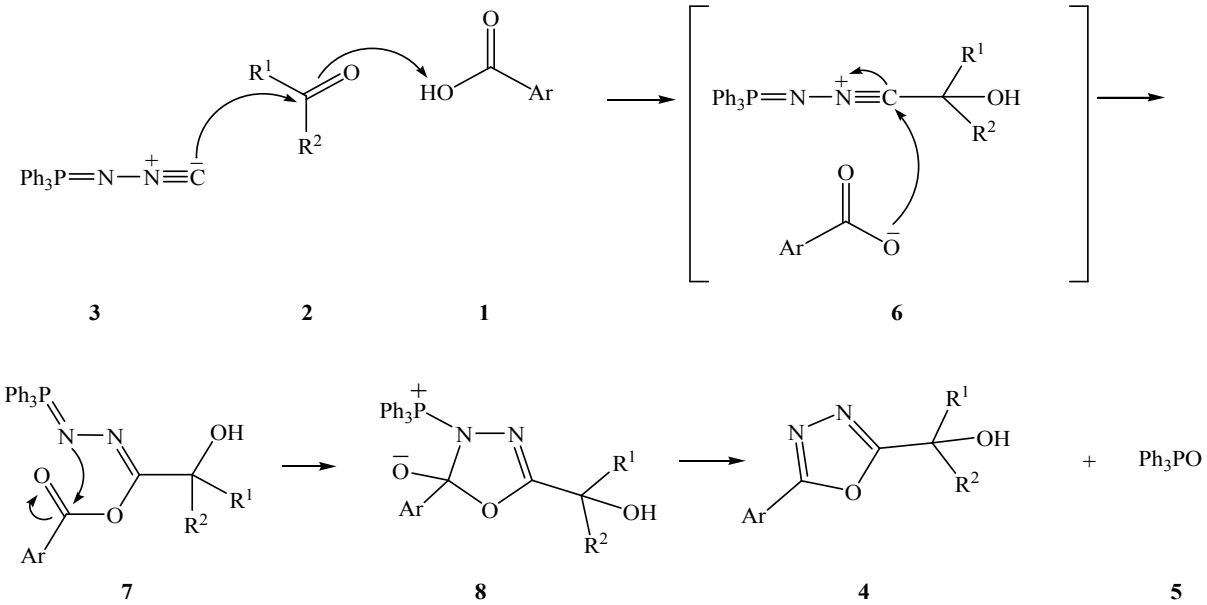
1-chloro-2-(5-m-tolyl-1,3,4-oxadiazol-2-yl)propan-2-ol **(4h)**

White crystals; mp: 131.0-133.1 °C; Yield: 93%. IR (KBr) (υ_{max}, cm^{-1}): 3365 (br), 1598, 1097. Anal.Calcd for $C_{12}H_{13}ClN_2O_2$ (252.70): C, 57.04; H, 5.19; N, 11.09 %. Found: C, 57.09; H, 5.16; N, 11.16 %. ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H 1.82 and 2.44 (2s, 6H, $2CH_3$), 3.85 (s, OH, exchanged by D_2O addition), 3.91 and 4.03 (AB-quartet, $^2J_{HH}$ = 11.37 Hz, 2H, CH_2Cl), 7.37 - 7.88 (m, 4H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 21.33 and 24.63 ($2CH_3$), 51.77 (C aliphatic), 71.05 (CH_2Cl), 123.28 and 139.02 (2C, arom), 124.20, 127.54, 129.0 and 132.86 (4CH, arom), 165.81 and 166.91 (2 C=N).

Results and discussion

The structures of the products were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4a** shows a singlet signal for two CH_2Cl groups (δ= 1.93), a broad singlet for OH (δ= 3.66, exchangeable by D_2O) and two doublet for aromatic protons (δ= 7.67 and 7.94, $^3J_{HH}$= 8.12 Hz). The ^{1}H decoupled ^{13}C NMR spectrum of **4a** shows 8 distinct resonances, partial assignment of these resonances is given in the experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **4b–h** were similar to those of **4a**, except for the aromatic and aliphatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

A mechanistic rationalization 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 the *α*- chloroketones **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 intramolecular aza-Wittig [12] reaction of iminophosphorane moiety with the ester carbonyl to afford the isolated disubstituted 1,3,4-oxadiazoles **4** by removal of triphenylphosphine oxide **5** from intermediate **8**.



Scheme 2. A proposed mechanism for the formation of disubstituted 1,3,4-oxadiazole derivatives **4a-h**.

Conclusion

We believe that the reported method offers a mild, simple, and efficient route for the preparation of disubstituted 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.

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