Reaction between *N*-Isocyaniminotriphenylphosphorane, Aldehydes, and Carboxylic Acids: A One-Pot and Three-Component Synthesis of 2-Aryl-5-hydroxyalkyl-1,3,4-oxadiazoles

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Abstract: A one-pot and three-component synthesis of 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles is described. *N*-Isocyaniminotriphenylphosphorane, an aldehyde, and a carboxylic acid undergo a 1:1:1 addition reaction under mild conditions to afford the title compounds in good yields.

Key words: 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles, *N*-isocyaniminotriphenylphosphorane, aldehydes, carboxylic acids, three-component reactions, cyclizations, heterocycles

Multicomponent reactions (MCR) have become a significant part of today's arsenal of methods in combinatorial chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCR is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] Multicomponent reactions, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCR are especially important in this area.[1d,e]

Nitrogen–oxygen heterocycles are of synthetic interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. The interest in five-membered systems containing one oxygen and two nitrogen atoms (positions 1, 3, and 4) stems from the occurrence of saturated and partially saturated 1,3,4-oxadiazoles in biologically active compounds and natural products. Compounds containing 1,3,4-oxadiazole moiety have been shown to possess a wide range of pharmacological and therapeutic activities.[2,3] 2-Aryl-5-hydroxymethyl-1,3,4-oxadiazoles **1** (Figure 1) have exhibited analgesic, anti-inflammatory, anticonvulsant, tranquilizing, myorelaxant, antidepressant, vasodilatatory, diuretic, antiulcer, antiarythmic, antiserotoninic, spasmolytic, hypotensive, antibronchocontrictive, anticholinergic, and antiemetic activities.[4] Furthermore, many 1,3,4-oxadiazole derivatives have been reported as active inhibitors of several enzymes.[2,3]

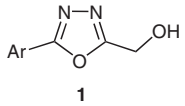

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Figure 1

Some 1,3,4-oxadiazoles have potential applications as photosensitizers,[5] liquid crystals,[6] ionic liquid solvents,[7] and organic light-emitting devices.[8] Some examples have also photomechanic,[9] photoluminescent, and electrochromic properties.[10,11]

So far, the most common synthetic methods reported for the preparation of 1,3,4-oxadiazoles involve: i) transformation of an existing heterocycle and ii) cyclizations: a) single-bond formation: cyclodehydration of 1,2-diacylhydrazines, oxidative cyclization of acylhydrazones, cyclodesulfurization of thiosemicarbazides and b) formation of two bonds: condensation and then cyclization of hydrazides with carboxylic acids, acyl chlorides, esters, amides, trialkyl orthoesters, carbon disulfide, or other C–S-containing components, cyanogen bromide, potassium isocyanate, trichloromethylarenes, and imidoyl chlorides.[2,3,12]

There are several reports on the use of *N*-isocyaniminotriphenylphosphorane ($NCNPPh_3$) **2** (Scheme 1) in the synthesis of metal complexes.[13,14] However, applications of **2** in organic synthesis are rare. Recently, a synthesis of 1,3,4-oxadiazepines has been reported via a three-component reaction between **2**, dialkyl acetylenedicarboxylates, and 1,3-diphenyl-1,3-propanedione.[15] A synthesis of 2-aryl-1,3,4-oxadiazoles from **2** and benzoic acids[16] has been reported.

Due to the unique properties of 2,5-disubstituted 1,3,4-oxadiazoles, the development of synthetic methods which enable facile access to these useful entities are desirable. As part of our current studies on the development of efficient and facile methods for the preparation of biologically active heterocyclic compounds,[17] we report herein a new synthesis of 1,3,4-oxadiazoles. Thus, a mixture of *N*-isocyaniminotriphenylphosphorane **2**, an excess of an aldehyde **3**, and a carboxylic acid **4** undergo a 1:1:1 addition reaction in CH_2Cl_2 at ambient temperature to produce the

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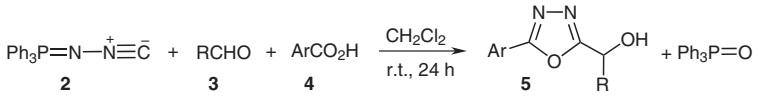
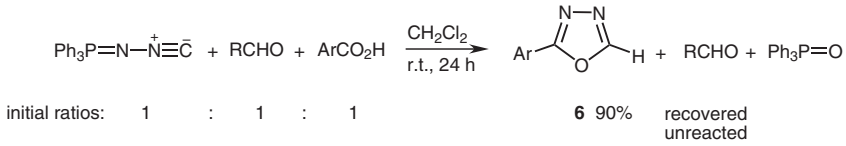


Scheme 1



Scheme 2

corresponding 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles **5** in 80–87% yields (Scheme 1, Table 1).

Table 1 Synthesis of 2-Aryl-5-hydroxyalkyl-1,3,4-oxadiazoles **5a–i**

5	R	Ar	Yield (%)[a]
5a	Me	4-BrC_6H_4	87
5b	Me	4-MeC_6H_4	84
5c	Me	4-ClC_6H_4	85
5d	Ph	4-ClC_6H_4	80
5e	$EtCH_2$	4-$Me_2NC_6H_4$	80
5f	4-$O_2NC_6H_4$	4-FC_6H_4	84
5g	3-$O_2NC_6H_4$	4-$MeOC_6H_4$	85
5h	Ph	4-BrC_6H_4	81
5i	2-naphthyl	9-anthryl	80

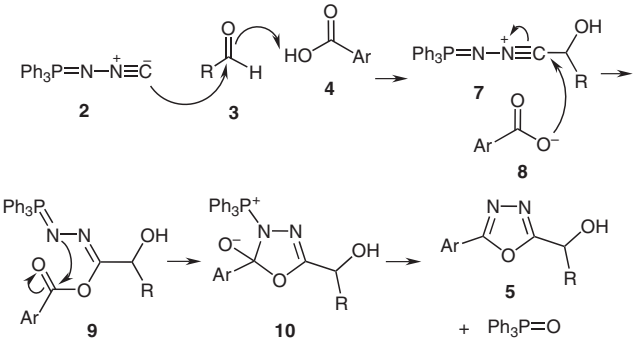
[a] Isolated yields.

When the reaction was performed using equivalent ratios of the three components, TLC and ^{1}H NMR analysis of the reaction mixture indicated formation of the corresponding 2-aryl-1,3,4-oxadiazole **6** in nearly 90% yield along with triphenylphosphine oxide, as has been previously reported,[16] and the aldehyde was recovered unreacted at the end of the reaction (Scheme 2). The best results were obtained when the reactions were carried out using the three components in a ratio of 1:4:1, respectively.[18]

All the reactions went to completion within 24 hours. The ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of the corresponding 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles **5** and triphenylphosphine oxide.[18]

The structures of the isolated products **5** were deduced by means of IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The IR spectrum of **5a** showed absorption at 3252 cm^{-1} indicating the presence of hydroxyl group. The mass spectrum of **5a** displayed the molecular ion [M$^+$] peaks at *m/z* = 270 [^{81}Br] and 268 [^{79}Br], which is consistent with the 1:1:1 adduct of *N*-isocyaniminotriphenylphosphorane, 4-bromobenzoic acid, and acetaldehyde losing triphenylphosphine oxide. The ^{1}H NMR spectrum of **5a** consisted of a doublet for the methyl group (δ = 1.53 ppm, J = 6.6 Hz), a multiplet for the methine H atom (δ = 4.99 ppm), and a doublet for the hydroxyl group (δ = 6.04 ppm, J = 5.6 Hz) due to coupling with the adjacent methinic H atom, along with two doublets for the four aromatic H atoms. The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** showed two distinct resonances at δ = 20.87 ppm for the methyl group and δ = 60.33 ppm arising from the methine carbon atom along with two deshielded characteristic resonances at δ = 163.23 and 168.81 ppm for the two oxadiazoles' carbon atoms, as well as other four signals for the aryl substituent in agreement with the proposed structure.[18]

A mechanistic rationalization for this reaction is provided in Scheme 3. On the basis of the chemistry of isocyanides,[1d,e,19,20] it is reasonable to assume that the first step may involve nucleophilic addition of the isocyanide **2** to the aldehyde **3**, which facilitates by its protonation with the acid **4**, leading to nitrilium intermediate **7**. This intermediate may be attacked by conjugate base of the acid **8** to form 1:1:1 adduct **9**. This adduct may undergo intramolecular aza-Wittig reaction of iminophosphorane moiety with the ester carbonyl to afford the isolated 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles **5** by removal of triphenylphosphine oxide from betaine intermediate **10**.



Scheme 3

In conclusion, we have developed a one-pot, three-component reaction between *N*-isocyanimino-triphenylphosphorane, aldehydes, and carboxylic acids for the preparation of 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles which are of potential synthetic and pharmacological interest. Good yields of the products and mild reaction conditions are the main advantages of this method. The

reactions were performed under neutral conditions, and the starting materials and reagents were simply mixed without any activation or modification. The simplicity of this method makes it an interesting alternative to other 1,3,4-oxadiazole syntheses. This approach is an extension of the previously described method which leads to oxadiazoles of type **6**, unsubstituted at C-5. The 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles prepared in the present study may find useful applications in synthetic organic, bioorganic, and medicinal chemistry.

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(18) **Procedure for the Preparation of 2-(4-Bromophenyl)-5-(1-hydroxyethyl)-1,3,4-oxadiazole (5a)**
A mixture of *N*-isocyaniminotriphenylphosphorane (0.302 g, 1 mmol), acetaldehyde (0.176 g, 4 mmol), 4-bromobenzoic acid (0.201 g, 1 mmol) in CH_2Cl_2 (4 mL) was stirred at ambient temperature for 24 h. Then, the solvent was removed, and the residue was purified by column chromatography using *n*-hexane–EtOAc (5:1) as eluent. The solvent was removed, and the product was obtained as colorless crystals. Yield 0.23 g (87%); mp 98 °C. IR (KBr): 3252 (OH), 1609, 1585, 1563, 1551, 1487, 1408, 1375, 1238, 1124, 1092, 1043, 1007, 841, 727 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 1.53 (d, *J* = 6.6 Hz, 3 H, CH_3), 4.99 (m, 1 H, C*H*CH_3), 6.04 (d, *J* = 5.6 Hz, 1 H, OH), 7.65 (d, *J* = 8.5 Hz, 2 H, 2 × CH), 7.98 (d, *J* = 8.5 Hz, 2 H, 2 × CH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 20.87 (CH_3), 60.33 (CH), 122.29 (C), 128.29 and 129.61 (2 × CH), 136.71 (C), 163.23 and 168.81 (2 × OC=N). MS: *m/z* (%) = 270 (2) [$M^{+\ 81}$Br], 268 (2) [$M^{+\ 79}$Br], 244 (16), 224 (97), 209 (24), 181 (72), 152 (40), 139 (100), 125 (20), 111 (56), 89 (18), 75 (36). Anal. Calcd for $C_{10}H_9BrN_2O_2$ (269.10): C, 44.63; H, 3.37; N, 10.41. Found: C, 44.5; H, 3.5; N, 10.2.

2-[4-(Dimethylamino)phenyl]-5-(1-hydroxypropyl)-1,3,4-oxadiazole (5e)
Yield 0.21 g (80%); colorless crystals; mp 118 °C. IR (KBr): 3219 (OH), 1610, 1582, 1553, 1502, 1433, 1371, 1198, 1173, 1128, 1085, 1014, 968, 810 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 0.89 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.27–1.47 (m, 2 H, CH_2), 1.78–1.84 (m, 2 H, CH_2), 2.98 [s, 6 H, $N(CH_3)_2$], 4.75–4.80 (m, 1 H, CH), 5.93 (d, *J* = 5.7 Hz, 1 H, OH), 6.80 (d, *J* = 8.9 Hz, 2 H, 2 × CH), 7.76 (d, *J* = 8.9 Hz, 2 H, 2 × CH). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 13.55 (CH_3), 17.98 and 36.57 (2 × CH_2), 39.56 [$N(CH_3)_2$], 63.87 (CH), 109.89 (C), 111.72 and 127.65 (2 × CH), 152.20 (C), 164.48 and 166.79 (2 × OC=N). MS: *m/z* (%) = 261 (100) [M^+], 218 (24), 188 (3), 160 (8), 146 (54), 132 (6), 118 (5), 105 (4), 91 (3), 77 (5). Anal. Calcd for $C_{14}H_{19}N_3O_2$ (261.32): C, 64.35; H, 7.33; N, 16.08. Found: C, 64.2; H, 7.4; N, 16.0.

5-[1-Hydroxy-1-(3-nitrophenyl)methyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (5g)
Yield 0.28 g (85%); colorless crystals; mp 148 °C. IR (KBr): 3190 (OH), 1614, 1591, 1537, 1504, 1477, 1442, 1350, 1265, 1174, 1049, 1022, 833, 800, 732 cm^{-1}. ^1H NMR (500.1 MHz, DMSO-d_6): δ = 3.82 (s, 3 H, OCH_3), 6.29 (d, *J* = 6.2 Hz, 1 H, CH), 7.11 (d, *J* = 8.7 Hz, 2 H, 2 × CH), 7.12 (d, *J* = 6.2 Hz, 1H, OH), 7.71 (t, *J* = 7.9 Hz, 1 H, CH), 7.90 (d, *J* = 8.7 Hz, 2 H, 2 × CH), 7.97 (d, *J* = 7.6 Hz, 1 H, CH), 8.21 (d, *J* = 8.0 Hz, 1 H, CH), 8.41 (s, 1 H, CH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 55.46 (OCH_3), 65.32 (CH), 114.87 (CH), 115.39 (C), 121.23, 123.03, 128.38, 129.97 and

133.27 (5 × CH), 141.59 and 147.80 (2 × C), 162.11 (CO), 164.36 and 166.18 (2 × OC=N). MS: *m/z* (%) = 327 (54) [M$^+$], 175 (91), 150 (13), 133 (100), 104 (15), 92 (14), 76 (28). Anal. Calcd for $C_{16}H_{13}N_3O_5$ (327.30): C, 58.72; H, 4.00; N, 12.84. Found: C, 58.7; H, 3.9; N, 12.8.

2-(9-Anthryl)-5-[1-hydroxy-1-(2-naphthyl)methyl]-1,3,4-oxadiazole (5i)

Yield 0.32 g (80%); colorless crystals; mp 176 °C. IR (KBr): 3250 (OH), 1601, 1566, 1550, 1508, 1454, 1415, 1375, 1269, 1175, 1142, 1082, 1003, 991, 889, 727 cm^{-1}. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ = 6.44 (d, *J* = 4.4 Hz, 1 H, CH), 7.06 (d, *J* = 4.4 Hz, 1 H, OH), 7.48–7.60 (m, 6 H, 6 × CH), 7.73 (d, *J* = 8.4 Hz, 1 H, CH), 7.79 (d, *J* = 8.3 Hz, 2 H, 2 × CH), 7.91–8.00 (m, 3 H, 3 × CH), 8.15 (s, 1 H, CH), 8.20 (d, *J* = 8.0 Hz, 2 H, 2 × CH), 8.92 (s, 1 H, CH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 66.77 (CH), 116.40 (C), 124.25, 124.55, 125.38, 125.89, 126.34, 126.41, 127.58, 127.97, 128.12, 128.13, 128.89 and 130.42 (12 × CH), 130.44, 131.66, 132.72, 132.75 and 136.99 (5 × C), 162.47 and 168.64 (2 ×°C=N). MS: *m/z* (%) = 402 (89) [M$^+$], 246 (7), 218 (7), 203 (100), 190 (16), 177 (16), 157 (54), 129 (49). Anal. Calcd for $C_{27}H_{18}N_2O_2$ (402.45): C, 80.58; H, 4.51; N, 6.96. Found: C, 80.7; H, 4.3; N, 6.8.

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