

The Reaction of (*N*-isocyanimino) triphenylphosphorane with an Electron-poor α -Haloketone in the Presence of Aromatic Carboxylic Acids: A Novel Three-Component Reaction for the Synthesis of Disubstituted 1,3,4-oxadiazole Derivatives

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ABSTRACT: Reactions of electron-poor α -haloketones with (*N*-isocyanimino) triphenylphosphorane in the presence of aromatic carboxylic acids proceed smoothly at room temperature and in neutral conditions to afford disubstituted 1,3,4-oxadiazole derivatives in high yields. © 2010 Wiley Periodicals, Inc. *Heteroatom Chem* 21:368–372, 2010; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20626

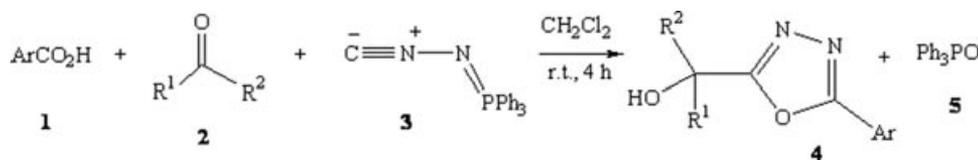
INTRODUCTION

Multicomponent reaction (MCR) is a chemical reaction where three or more compounds react to form a single product. By definition, MCRs are those reactions whereby more than two reactants combine in a sequential manner to give highly selective products that retain majority of the atoms of the starting

material. The development of novel MCRs is receiving growing interest from industrial chemistry research groups and represents a challenge for organic chemists [1,2]. The drive toward the ideal synthesis embracing the step count, ideally just one, and yield, ideally 100%, has been pursued aggressively since scientists began to construct molecules. Of course, there are many other factors that affect these two aspects of synthesis, including cost; starting material availability; safety; environmental concerns; and overall ease of the process, including work-up and purification [3]. The nature of the synthesis project also plays a role. Complex molecule total synthesis is often driven by step count while showcasing innovative chemistry. Traditional structure-activity relationship evaluations in medicinal chemistry typically involve the preparation of an advanced intermediate that can be analogued readily to introduce the molecular diversity necessary to prepare a collection, or library, of structurally related compounds. One strategy that potentially meets the goals of total synthesis and library production is MCR chemistry, in which three or more starting materials are brought together in a highly convergent approach to rapidly build up molecular structure and complexity [4].

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

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, antifungal, anti-inflammatory, and antihypertensive [5–9].

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multistep in nature [10–15]. 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 [16–21].

In recent years, several synthetic methods have been reported for the preparation of (*N*-isocyanimino)triphenylphosphorane (CNNPPh₃) **3** [22–23]. There are several reports on the use of (*N*-isocyanimino)triphenylphosphorane (CNNPPh₃) **3** in the synthesis of metal complexes [22–23]. However, application of **3** in the synthesis of organic compounds is fairly rare [24–31]. As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds [24–31], we sought to develop a convenient preparation of disubstituted 1,3,4-oxadiazole derivatives **4a–k**. Herein, we report a hitherto unknown, one-pot, three-component reaction, which, starting from readily available electron-poor α -haloketones **2**, affords disubstituted 1,3,4-oxadiazole derivatives **4a–k** (Scheme 1).

RESULTS AND DISCUSSION

The carboxylic acid derivative **1** with electron-poor α -haloketones **2** and (*N*-isocyanimino)triphenylphosphorane **3** in CH₂Cl₂ react together in a 1:1:1 ratio at room temperature to produce disubstituted 1,3,4-oxadiazole derivatives **4** and triphenylphosphine oxide **5** (Scheme 1 and Table 1). The reaction proceeds smoothly and cleanly under mild conditions, and no side reactions were observed. We

also used acetone **6a** and acetophenone **6b** instead of electron-poor α -haloketones **2** in this reaction, but no corresponding products **4** were observed. In both the cases, 2-aryl-1,3,4-oxadiazoles **7** and triphenylphosphine oxide **5** were observed, as has been previously reported [25], and the acetone **6a** and acetophenone **6b** were recovered unreacted at the end of reaction (Scheme 2). As indicated in Table 1, the reactions proceeded efficiently with an electron-poor ketone **2** and electron-rich ketones such as acetone **6a** and acetophenone **6b** are not suitable starting materials in these reactions (Scheme 2).

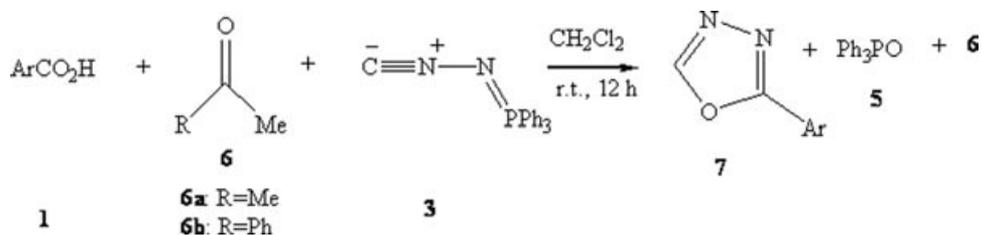
The structures of the products were deduced from their IR, Mass, ¹H NMR, and ¹³C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ¹H NMR spectrum of **4a** consisted of a singlet for the CH₃ (δ = 1.93), a hydroxy hydrogen atom (δ = 4.51, exchangeable by D₂O) and two doublets for the aromatic protons (δ = 7.50 and 7.99, ³*J*_{HH} = 8.5 Hz). The ¹H decoupled ¹³C NMR spectrum of **4a** showed nine distinct resonances, partial assignment of these resonances is given in the Experimental section. The ¹H and ¹³C NMR spectra of compounds **4b–k** were similar to those of **4a**, except for the aromatic and aliphatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

TABLE 1 Synthesis of Disubstituted 1,3,4-oxadiazole Derivatives **4** (Scheme 1)

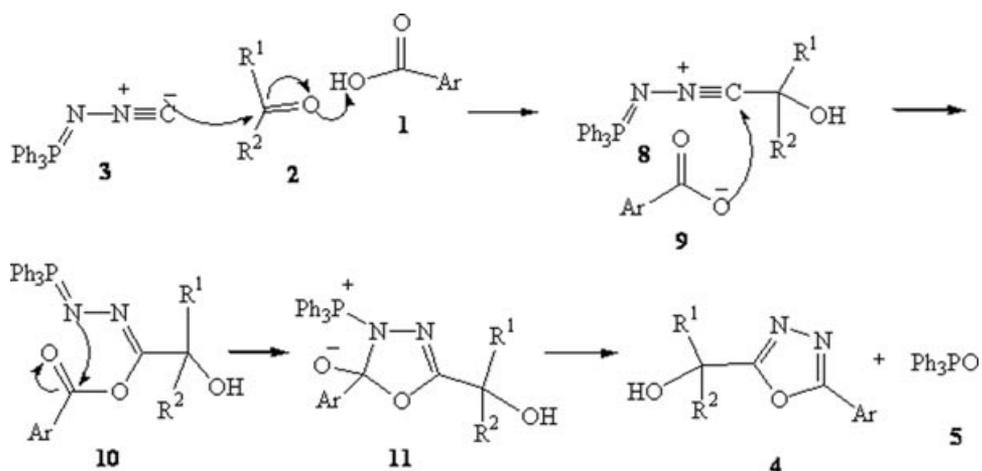
4	Ar	R ¹	R ²	% Yield ^{a,b}
a	4-ClC ₆ H ₄	CH ₃	CF ₃	85
b	3-ClC ₆ H ₄	CH ₃	CF ₃	83
c	4-BrC ₆ H ₄	CH ₃	CF ₃	84
d	3-FC ₆ H ₄	CH ₃	CF ₃	85
e	C ₆ H ₅	CH ₃	CF ₃	85
f	4-MeC ₆ H ₄	CH ₃	CF ₃	87
g	3-MeOC ₆ H ₄	CH ₃	CF ₃	88
h	C ₆ H ₅	CH ₃	CH ₂ Cl	84
i	C ₆ H ₅	CH ₃	CHCl ₂	85
j	C ₆ H ₅	CH ₂ Cl	CH ₂ Cl	88
k	4-MeC ₆ H ₄	CH ₂ Cl	CH ₂ Cl	87

^aWe also used acetone **6a** and acetophenone **6b** instead of electron-poor ketone **2** in this reaction, but no corresponding products **4** were observed (Scheme 2).

^bIsolated yields.



SCHEME 2 Electron-rich ketones such as acetone **6a** and acetophenone **6b** are not suitable starting materials in the three-component synthesis of 1,3,4-oxadiazole derivatives.



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

A mechanistic rationalization for this reaction is provided in Scheme 3. On the basis of the chemistry of isocyanides [4], it is reasonable to assume that the first step may involve nucleophilic addition of the (*N*-isocyanimino)triphenylphosphorane **3** to the electron-poor ketone **2**, which facilitates by its protonation with the acid **1**, leading to nitrilium intermediate **8**. This intermediate may be attacked by conjugate base of the acid **9** to form 1:1:1 adduct **10**. This adduct may undergo intramolecular aza-Wittig [32] 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 **11**.

CONCLUSIONS

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.

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. ^1H 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. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values.

GENERAL PROCEDURE FOR THE PREPARATION OF COMPOUNDS **4a-k**; GENERAL PROCEDURE EXEMPLIFIED FOR **4a**

To a stirred solution of (*N*-isocyanimino)triphenylphosphorane (1 mmol) and 1,1,1-trifluoroacetone (1 mmol) in CH_2Cl_2 (7 mL) was

added dropwise a solution of 4-chlorobenzoic acid (1 mmol) 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-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-1,1,1-trifluoro-2-propanol (4a): White crystals; mp: 145.5–147.1°C; Yield: 85%. IR (KBr) (ν_{max} , cm^{-1}): 3281, 1607, 1488, 1159, 1095, 716. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.93 (s, 3H, CH_3), 4.51 (s, 1H, OH, exchanged by D_2O addition), 7.50 (d, $^3J_{\text{HH}} = 8.5$ Hz, 2H, arom), 7.99 (d, $^3J_{\text{HH}} = 8.5$ Hz, 2H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 20.46 (CH_3), 72.32 (q, $^2J_{\text{CF}} = 32.2$ Hz, $\text{C}-\text{CF}_3$), 121.76 and 139.22 (2C, arom), 123.90 (q, $^1J_{\text{CF}} = 286.1$ Hz, CF_3), 128.80 and 129.96 (4CH, arom), 164.19 and 166.03 (2C=N). Anal. Calcd for $\text{C}_{11}\text{H}_8\text{ClF}_3\text{N}_2\text{O}_2$ (292.6): C, 45.15; H, 2.76; N, 9.57%. Found: C, 45.22; H, 2.71; N, 9.50. MS: m/z (%) (EI) 294 ($[\text{M}^+ + 2]$, 24), 292 (M^+ , 54), 225 (27), 223 (63), 183 (33), 181 (100), 139 (62), 111 (51), 74 (51), 62 (26), and 43 (84).

2-[5-(3-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-1,1,1-trifluoro-2-propanol (4b): Yellow crystals; mp: 87.0–88.8°C; Yield: 83%. IR (KBr) (ν_{max} , cm^{-1}): 3477, 1561, 1478, 1159, 1105, 720. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.93 (s, 3H, CH_3), 4.29 (s, 1H, OH, exchanged by D_2O addition), 7.35–8.12 (m, 4H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 20.52 (CH_3), 72.34 (q, $^2J_{\text{CF}} = 32.1$ Hz, $\text{C}-\text{CF}_3$), 123.91 (q, $^1J_{\text{CF}} = 285.6$ Hz, CF_3), 124.87 and 135.71 (2C, arom), 125.64, 127.48, 130.92 and 132.87 (4CH, arom), 164.53 and 165.62 (2C=N). Anal. Calcd for $\text{C}_{11}\text{H}_8\text{ClF}_3\text{N}_2\text{O}_2$ (292.6): C, 45.15; H, 2.76; N, 9.57%. Found: C, 45.09; H, 2.80; N, 9.50. MS: m/z (%) (EI) 292 (M^+ , 4), 223 (5), 138 (33), 113 (19), 110 (32), 91 (19), 74 (55), 69 (48), and 42 (100).

2-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]-1,1,1-trifluoro-2-propanol (4c): White crystals; mp: 153.6–155.5°C; Yield: 84%. IR (KBr) (ν_{max} , cm^{-1}): 3237, 1602, 1484, 1158, 1078, 727. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.93 (s, 3H, CH_3), 4.16 (s, 1H, OH; exchanged by D_2O addition), 7.68 (d, $^3J_{\text{HH}} = 8.0$ Hz, 2H, arom), 7.93 (d, $^3J_{\text{HH}} = 8.0$ Hz, 2H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 20.44 (CH_3), 72.32 (q, $^2J_{\text{CF}} = 32.1$ Hz, $\text{C}-\text{CF}_3$), 122.21 and 127.67 (2C, arom), 123.88 (q, $^1J_{\text{CF}} = 286.2$ Hz, CF_3), 128.90 and 132.93 (4CH, arom), 164.19 and 166.14 (2C=N). Anal. Calcd for $\text{C}_{11}\text{H}_8\text{BrF}_3\text{N}_2\text{O}_2$ (337.1): C, 39.19; H, 2.39; N, 8.31%. Found: C, 39.13; H, 2.43; N, 8.24. MS: m/z (%) (EI) 338 ($[\text{M}^+ + 2]$, 65), 336 (M^+ , 64), 269 (64),

225 (100), 197 (14), 183 (55), 155 (29), 102 (33), 75 (32), and 43 (71).

1,1,1-Trifluoro-2-[5-(3-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-propanol (4d): Yellow crystals; mp: 95.1–97.0°C; Yield: 85%. IR (KBr) (ν_{max} , cm^{-1}): 3280, 1605, 1165, 1087, 776. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.93 (s, 3H, CH_3), 4.34 (s, 1H, OH, exchanged by D_2O addition), 7.23–7.88 (m, 4H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 20.48 (CH_3), 72.33 (q, $^2J_{\text{CF}} = 32.1$ Hz, $\text{C}-\text{CF}_3$), 114.60 (d, $^2J_{\text{CF}} = 24.5$ Hz, CH, arom), 119.93 (d, $^2J_{\text{CF}} = 20.8$ Hz, CH, arom), 123.33 (d, $^4J_{\text{CF}} = 3.8$ Hz, CH, arom), 123.90 (q, $^1J_{\text{CF}} = 285.6$ Hz, CF_3), 125.11 (d, $^3J_{\text{CF}} = 8.2$ Hz, C, arom), 131.44 (d, $^3J_{\text{CF}} = 8.2$ Hz, CH, arom), 163.14 (d, $^1J_{\text{CF}} = 248.5$ Hz, C, arom), 164.47 and 165.85 (2C=N). Anal. Calcd for $\text{C}_{11}\text{H}_8\text{F}_4\text{N}_2\text{O}_2$ (276.2): C, 47.84; H, 2.92; N, 10.14%. Found: C, 47.90; H, 2.95; N, 10.11. MS: m/z (%) (EI) 276 (M^+ , 7), 207 (9), 165 (22), 123 (100), 95 (63), 75 (30), 69 (18), and 42 (68).

1,1,1-Trifluoro-2-(5-phenyl-1,3,4-oxadiazol-2-yl)-2-propanol (4e): White crystals; mp: 120.0–121.4°C; Yield: 85%. IR (KBr) (ν_{max} , cm^{-1}): 3320, 1560, 1156, 1084, 708. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.94 (s, 3H, CH_3), 5.08–5.35 (br. s, 1H, OH; exchanged by D_2O addition), 7.41–7.68 (m, 3H, arom), 8.04 (d, $^3J_{\text{HH}} = 7.0$ Hz, 2H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 21.22 (CH_3), 72.92 (q, $^2J_{\text{CF}} = 32.1$ Hz, $\text{C}-\text{CF}_3$), 123.81 (C, arom), 124.65 (q, $^1J_{\text{CF}} = 286.2$ Hz, CF_3), 128.17, 130.15 and 133.46 (5CH, arom), 165.04 and 167.35 (2C=N). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{N}_2\text{O}_2$ (258.2): C, 51.17; H, 3.51; N, 10.85%. Found: C, 51.15; H, 3.55; N, 10.81. MS: m/z (%) (EI) 258 (M^+ , 9), 189 (16), 147 (25), 105 (81), 90 (9), 77 (100), 63 (14), and 43 (53).

1,1,1-Trifluoro-2-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]-2-propanol (4f): Yellow crystals; mp: 111.7–113.6°C; Yield: 87%. IR (KBr) (ν_{max} , cm^{-1}): 3238, 1502, 1160, 1109, 725. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.92 and 2.42 (2s, 6H, 2 CH_3), 5.08–5.35 (br. s, 1H, OH; exchanged by D_2O addition), 7.30 (d, $^3J_{\text{HH}} = 7.9$ Hz, 2H, arom), 7.92 (d, $^3J_{\text{HH}} = 7.9$ Hz, 2H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 20.55 and 22.02 (2 CH_3), 72.26 (q, $^2J_{\text{CF}} = 32.1$ Hz, $\text{C}-\text{CF}_3$), 120.40 and 143.53 (2C, arom), 124.02 (q, $^1J_{\text{CF}} = 285.6$ Hz, CF_3), 127.49 and 130.20 (4CH, arom), 164.08 and 166.88 (2C=N). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_2$ (272.2): C, 52.94; H, 4.07; N, 10.29%. Found: C, 52.87; H, 4.09; N, 10.35. MS: m/z (%) (EI) 272 (M^+ , 100), 203 (84), 161 (79), 160 (76), 136 (19), 119 (66), 91 (84), 77 (14), 65 (21), and 43 (31).

1,1,1-Trifluoro-2-[5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl]-2-propanol (4g): Yellow crystals; mp: 80.0–81.5°C; Yield: 88%. IR (KBr) (ν_{max} , cm^{-1}):

3475, 1607, 1468, 1147, 1080, 862. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.93 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.61–4.84 (br. s, 1H, OH; exchanged by D_2O addition), 7.11 (d, $^3J_{\text{HH}} = 8.2$ Hz, 1H, arom), 7.42 (t, $^3J_{\text{HH}} = 7.9$ Hz, 1H, arom), 7.58 (s, 1H, arom) 7.62 (d, $^3J_{\text{HH}} = 8.0$ Hz, 1H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 21.13 (CH_3), 56.53 (OCH_3), 72.91 (q, $^2J_{\text{CF}} = 32.1$ Hz, C– CF_3), 112.86, 119.79, 120.54 and 131.32 (4CH, arom), 124.92 and 160.94 (2C, arom), 124.61 (q, $^1J_{\text{CF}} = 286.2$ Hz, CF_3), 156.87 and 156.97 (2C=N). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_3$ (288.2): C, 50.01; H, 3.85; N, 9.72%. Found: C, 49.93; H, 3.87; N, 9.79. MS: m/z (%) (EI) 288 (M^+ , 9), 219 (4), 177 (9), 135 (23), 107 (10), 92 (5), 77 (14), 58 (24), and 43 (100).

1-Chloro-2-[(5-phenyl)-1,3,4-oxadiazol-2-yl]-2-propanol (4h): White crystals; mp: 83.5–84.7°C; Yield: 84%. IR (KBr) (ν_{max} , cm^{-1}): 3274 (br), 1655, 1560, 1125, 1083, 706. ^1H NR (CDCl_3 , 250 MHz): δ_{H} 1.82 (1 s, 3 H, CH_3), 1.91 (1 s, OH, exchanged by D_2O addition), 3.90 and 4.08 (AB-quartet, $^2J_{\text{HH}} = 11.3$ Hz, 2 H, CH_2Cl), 7.51–8.04 (m, 5 H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 24.59 (CH_3), 51.70 (CH_2Cl), 71.10 (CH aliphatic), 123.41 (C, arom), 127.05, 129.08 and 132.04 (5 CH, arom), 165.42 and 167.58 (2C=N).

1,1-Dichloro-2-[(5-phenyl)-1,3,4-oxadiazol-2-yl]-2-propanol (4i): White crystals; mp: 99.3–101.4°C; Yield: 85%. IR (KBr) (ν_{max} , cm^{-1}): 3188 (br), 1609, 1558, 1132, 779. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.96 (s, 3 H, CH_3), 4.40 (s, OH, exchanged by D_2O addition), 6.12 (s, 1 H, CHCl_2), 7.53–8.05 (m, 5 H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 22.11 (CH_3), 75.34 (CHCl_2), 77.54 (CH aliphatic), 123.16 (C, arom), 127.14, 129.14 and 132.24 (5 CH, arom), 165.64 and 166.02 (2C=N).

1,3-Dichloro-2-[(5-phenyl)-1,3,4-oxadiazol-2-yl]-2-propanol (4j): White crystals; mp: 107.1–108.9°C; Yield: 88%. IR (KBr) (ν_{max} , cm^{-1}): 3203 (br), 1613, 1561, 1142, 1084, 779. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 4.12 (1 s, 4 H, 2 CH_2Cl), 4.36 (1 s, OH, exchanged by D_2O addition), 7.53–8.05 (m, 5 H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 46.90 (2 CH_2Cl), 73.28 (CH aliphatic), 123.05 (C, arom), 127.18, 129.16 and 132.33 (5 CH, arom), 164.70 and 165.80 (2C=N).

1,3-Dichloro-2-[(5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl)-2-propanol (4k): White crystals; mp: 160–161.2°C; Yield: 87%. IR (KBr) (ν_{max} , cm^{-1}): 3106 (br), 1615, 1554, 1186, 1067, 781. ^1H NMR (CDCl_3 , 250 MHz): δ_{H} 1.82 (1 s, 3 H, CH_3), 1.91 (1 s, OH, exchanged by D_2O addition), 3.90 and 4.04 (AB-quartet, $^2J_{\text{HH}} = 11.5$ Hz, 4H, 2 CH_2Cl), 7.50–8.04 (m, 4 H, arom). ^{13}C NMR (CDCl_3 , 62.5 MHz): δ_{C} 24.59 (CH_3), 51.70 (2 CH_2Cl), 71.11 (CH aliphatic), 123.41 and 132.68 (2C, arom), 127.05, 128.82 and 132.04 (4 CH, arom), 165.42 and 167.59 (2C=N).

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