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One-pot, Three-component Synthesis of Fully Substituted 1,3,4-Oxadiazole Derivatives from (*N*-Isocyanoimino)triphenylphosphorane, Aromatic Carboxylic acids and (1*R*)-(−)-Campherchinon

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Reactions of (*N*-isocyanimino)triphenylphosphorane with (1*R*)-(−)-campherchinon in the presence of aromatic carboxylic acids proceed smoothly at room temperature and in neutral conditions to afford sterically congested 1,3,4-oxadiazole derivatives in high yields. The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed.

Key Words : (*N*-Isocyanimino)triphenylphosphorane, (1*R*)-(−)-Campherchinon, Aromatic carboxylic acid, 1,3,4-Oxadiazole, *aza*-Wittig reaction

Introduction

Multicomponent reactions (MCR) have appeared as an efficient and powerful tool in modern synthetic organic 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. Since all the organic reagents employed are consumed and incorporated into the target compound, purification of products resulting from MCR is also simple.[1] MCR, leading to interesting heterocyclic scaffolds, are especially useful for the construction of diverse chemical libraries of 'druglike' molecules. The isocyanide-based MCR are very important in this area.[2-4] Among the known multicomponent reactions to date, the most valuable reactions are those based on isocyanides. Isocyanide-based multicomponent reactions (abbreviated to IMCRs by Ugi and Dömling) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted considerable attention because of the advantages that they offer to the field of combinatorial chemistry.[5-7]

Camphor and also its derivatives are the most frequently employed types of chiral pool starting materials, building blocks, resolving agents, shift reagents in NMR spectroscopy, and ligands in various asymmetric reagents and catalysts.[8-10] Examples of highly enantioselective ligands for the dialkylzinc addition to aldehydes are Noyori's (−)-3-exo-dimethylaminoisoborneol [(−)-DAIB] (I) and its morpholino-modified analogue (II).[11,12] Also various camphor based *P,N*-ligands (III) were used in asymmetric hydrogenations.[13,14] Additionally, some of the camphor derivatives show interesting biological activities. For example camphorsulphonylbenzimidazoles (V) have antibacterial effect and antispasmodic aminoketone (IV) has been applied in the pharmaceutical field (Figure 1).[15,16]

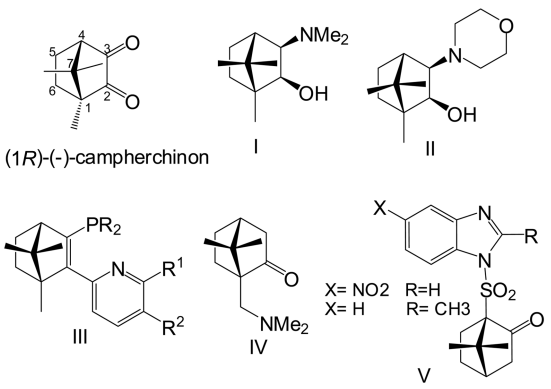


Figure 1. Some examples of camphor derivatives.

In recent years there has been considerable investigation on different classes of oxadiazoles. Particularly, compounds containing 1,3,4-oxadiazole nucleus have been shown to possess a wide range of pharmacological and therapeutic activities. Some 1,3,4-oxadiazoles have shown analgesic, *anti*-inflammatory, anticonvulsant, tranquilizing, myorelaxant, antidepressant, vasodilatatory, diuretic, antiulcer, antiarythmic, antiserotoninic, spasmolytic, hypotensive, antibronchocontrictive, anticholinergic, and antiemetic activities. Additionally, many 1,3,4-oxadiazole derivatives have been reported as active inhibitors of several enzymes (Figure 2).[17-20]

Recently, the intramolecular version of the *aza*-Wittig-type reaction has attracted much attention because it has exhibited 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. Existence of the nucleophilicity at the nitrogen is a factor of essential mechanistic importance in the use of these iminophosphoranes as *aza*-Wittig reagents. Iminophosphoranes are important reagents in

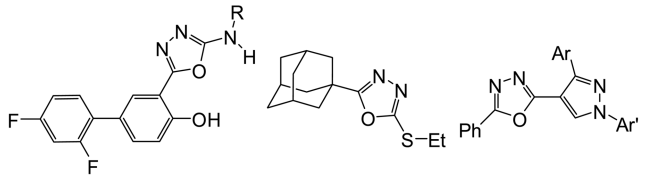


Figure 2. Examples of some biologically active 2,5-disubstituted 1,3,4-oxadiazole derivatives.

synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity.[21,22] However, the organic chemistry of (*N*-isocyanimino)triphenylphosphorane **3** remains almost unexplored. (*N*-Isocyanimino)triphenylphosphorane **3** is expected to have synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality.[21,22] In recent years, we have established a one-pot method for the synthesis of organophosphorus compounds.[23-25] In this paper, we report an interesting three-component reaction of (*N*-isocyanimino)triphenylphosphorane **3** (Scheme 1).

Experimental

(*N*-Isocyanimino)triphenylphosphorane **3** was prepared based on reported procedures.[22] Other 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 are TLC and NMR. TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H and ^{13}C-NMR spectra ($CDCl_3$) were recorded on a BRUKER DRX-250AVANCE 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 70 eV. Preparative thin layer chromatography was prepared from Merck silica gel (F_{254}) powder.

General Procedure for Compounds 4a-o. A mixture of (*N*-isocyanimino)triphenylphosphorane (0.30 g, 1 mmol), (1*R*)-(−)-campherchinon (0.15 g, 1 mmol) and aromatic carboxylic acid (1 mmol) in CH_3CN (5 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the viscous residue was purified by preparative layer chromatography (PLC) (silica gel (F_{254}) powder; petroleum ether-ethyl acetate (4:1). The characterization data of the compounds are given below.

3-Hydroxyl-1,7,7-trimethyl-3-(5-phenyl)-1,3,4-oxadiazol-2-yl]bicyclo[2.2.1]heptan-2-one (4a). White powder, yield: 90%, mp 173-175°. IR (KBr): 3283 (OH), 2961, 2928, 1762, 1606, 1548, 1485, 1088, 785, 690 cm^{-1}; ^{1}H NMR δ 7.50-8.03 (m, 5H, CH_{arom}), 3.65 (s, 1H, OH), 2.52 (s, 1H, CH), 1.68-1.91 (m, 4H, $2CH_2$), 1.05 (s, 3H, CH_3), 1.16 (s, 6H, $2CH_3$). ^{13}C NMR δ 213.00 (C=O), 166.76, 165.54 (2C=N), 131.95, 129.01, 127.10 (5CH), 123.21 (C), 77.65 (C-OH), 58.29 (C), 52.79 (CH), 46.22 (C), 27.96, 23.29 ($2CH_2$), 21.92, 20.42, 9.45 ($3CH_3$). MS *m/z* (%) 312 (M$^+$, 48), 269 (12), 241 (20), 202 (92), 187 (100), 147 (28), 105 (40), 83 (44), 77 (48), 55 (56), 41 (32). Anal. Calcd for $C_{18}H_{20}N_2O_3$ (312.15): C 69.21, H 6.45, N 8.97. Found: C 69.15, H 6.51, N 9.03.

3-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4b). White powder, yield: 88%, mp 127-129°. IR (KBr): 3354 (OH), 2960, 2928, 1762, 1606, 1547, 1458, 1100, 843 cm^{-1}; ^{1}H NMR δ 7.95 (d, $^3J_{HH}$ = 6.5 Hz, 2H, CH_{arom}), 7.45 (d, $^3J_{HH}$ = 6.5 Hz, 2H, CH_{arom}), 3.75 (s, 1H, OH), 2.51 (m, 1H, CH), 1.73-1.91 (m, 4H, $2CH_2$), 1.04 (s, 3H, CH_3), 1.16 (s, 6H, $2CH_3$). ^{13}C NMR δ 213.01 (C=O), 165.74, 164.24 (2C=N), 138.30 (C), 129.40, 128.37 (4CH), 121.88 (C), 77.60 (C-OH), 58.29 (C), 52.75 (CH), 46.23 (C), 27.93, 23.31 ($2CH_2$), 9.43, 20.42, 21.93 ($3CH_3$). MS *m/z* (%) 346 (M$^+$, 32), 249 (20), 236 (48), 221 (64), 207 (32), 167 (28), 156 (36), 149 (96), 139 (100), 111 (56), 95 (48), 83 (68), 69 (56), 55 (72), 41 (64). Anal. Calcd for $C_{18}H_{19}ClN_2O_3$ (346.11): C 62.34, H 5.52, N 8.08. Found: C 62.39, H 5.47, N 8.03.

3-Hydroxyl-3-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4c). White powder, yield 87%, mp 177-179°. IR (KBr): 3275 (OH), 2963, 2934, 1765, 1616, 1503, 1455, 1084, 837 cm^{-1}; ^{1}H NMR δ 7.92 (d, $^3J_{HH}$ = 8.75 Hz, 2H, CH_{arom}), 6.94 (d, $^3J_{HH}$ = 8.75 Hz, 2H, CH_{arom}), 4.00 (s, 1H, OH), 3.85 (s, 3H, OCH_3), 2.46 (m, 1H, CH), 1.60-1.94 (m, 4H, $2CH_2$), 1.03 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR δ 213.08 (C=O), 165.18, 165.07 (2C=N), 162.41 (C), 128.87, 114.40 (4CH), 115.93 (C), 76.63 (C-OH), 55.47 (OCH_3), 58.52 (C), 52.83 (CH), 46.18 (C), 27.97, 23.29 ($2CH_2$), 21.92, 20.44, 9.45 ($3CH_3$). MS *m/z* (%) 342 (M$^+$, 40), 293 (16), 271 (16), 245 (24), 232 (36), 217 (100), 203 (48), 176 (36), 149 (56), 133 (84), 83 (24), 69 (28), 55 (32), 41 (20). Anal.Calcd for $C_{19}H_{22}N_2O_4$ (342.16): C 66.65, H 6.48, N 8.18. Found: C 66.60, H 6.43, N 8.123.

3-{5-[4-(Bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl}-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4d). White powder, yield 88%, mp 117-119°. IR (KBr): 3274 (OH), 2960, 2928, 1764, 1616, 1554, 1417, 1087, 858 cm^{-1}; ^{1}H NMR δ 7.99 (d, $^3J_{HH}$ = 7.2 Hz, 2H, CH_{arom}), 7.50 (d, $^3J_{HH}$ = 7.2 Hz, 2H, CH_{arom}), 4.50 (s, 2H, CH_2), 3.93 (s, 1H, OH), 2.51 (m, 1H, CH), 1.73-1.85 (m, 4H, $2CH_2$), 1.04 (s, 3H, CH_3), 1.17 (s, 6H, $2CH_3$). ^{13}C NMR δ 213.21 (C=O), 165.83, 164.85 (2C=N), 141.72 (2C), 129.68, 127.52 (4CH), 123.32 (C), 76.65 (C-OH), 58.28 (C), 52.79 (CH), 46.22 (C), 32.15 (CH_2Br), 27.95, 23.28 ($2CH_2$), 21.93, 20.42, 9.44 ($3CH_3$). MS *m/z* (%) 404 (M$^+$, 20), 296 (24), 279 (56), 214 (24), 159 (60),116 (100), 83 (48), 69 (36), 55 (80), 41 (56). Anal. Calcd for $C_{19}H_{21}BrN_2O_3$ (404.07): C 56.31, H 5.22, N 6.91. Found: C 56.36, H 5.17, N 6.86.

3-[5-(3,4-Dimethylphenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4e). White powder, yield 86%, mp 152-154°. IR (KBr): 3285 (OH), 2943, 2928, 1764, 1615, 1551, 1489, 1088, 856, 726 cm^{-1}; ^{1}H NMR δ 7.21-7.80 (m, 3H, CH_{arom}), 3.57 (s, 1H, OH), 2.48

(m, 1H, CH), 2.31 (s, 6H, $2CH_3$), 1.62-1.96 (m, 4H, $2CH_2$), 1.05 (s, 3H, CH_3), 1.16 (s, 6H, $2CH_3$). ^{13}C NMR δ 213.00 (C=O), 166.34, 165.20 (2C=N), 141.26, 137.51 (2C), 130.22, 128.05, 124.62 (3CH), 120.93 (C), 76.65 (C-OH), 58.26 (C), 52.80 (CH), 46.20 (C), 27.95, 23.30 ($2CH_2$), 19.94, 19.62 ($2CH_3$), 21.91 , 20.44, 9.45 ($3CH_3$). MS *m/z* (%) 340 (M^+, 68), 269 (24), 243 (48), 230 (28), 215 (88), 201 (92), 175 (24), 149 (36), 133 (100), 116 (32), 105 (44), 69 (40), 55 (40), 41 (44). Anal. Calcd for $C_{20}H_{24}N_2O_3$ (340.18): C 70.56, H 7.11, N 8.23. Found: C 70.50, H 7.17, N 8.17.

3-{5-[4-(Tert-butyl)phenyl]-1,3,4-oxadiazol-2-yl}-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4f). Colorless Oil, yield 87%, IR (KBr): 3408 (OH), 2963, 2871, 1762, 1615, 1500, 1458, 1112, 843 cm^{-1}; ^{1}H NMR δ 7.95 (d, $^3J_{HH}$ = 8.0 Hz, 2H, CH_{arom}), 7.49 (d, $^3J_{HH}$ = 8.0 Hz, 2H, CH_{arom}), 3.51 (s, 1H, OH), 2.47 (m, 1H, CH), 1.62-1.90 (m, 4H, $2CH_2$), 1.34 (s, 9H, $3CH_3$), 1.04 (s, 3H, CH_3), 1.17 (s, 6H, $2CH_3$). ^{13}C NMR δ 213.11 (C=O), 165.37 (2C=N), 155.62 (C), 126.95, 125.97 (4CH), 120.61(C), 76.66 (C-OH), 58.27 (C), 52.86 (CH), 46.20 (C), 35.06 (C), 31.07 ($3CH_3$), 27.98, 23.24 ($2CH_2$), 21.92, 20.43, 9.45 ($3CH_3$). Anal. Calcd for $C_{22}H_{28}N_2O_3$ (368.21): C 71.71, H 7.66, N 7.60. Found: C 71.76, H 7.61, N 7.65.

3-Hydroxyl-1,7,7-trimethyl-3-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]bicyclo[2.2.1]heptan-2-one (4g). White powder, yield 86%, mp 136-138º. IR (KBr): 3281 (OH), 2955, 2929, 1766, 1615, 1548, 1499, 1088, 823 cm^{-1}; ^{1}H NMR δ 7.89 (d, $^3J_{HH}$ = 6.25 Hz, 2H, CH_{arom}), 7.26 (d, $^3J_{HH}$ = 6.25 Hz, 2H, CH_{arom}), 3.73 (s, 1H, OH), 2.50 (s, 1H, CH), 2.40 (s, 3H, CH_3), 1.67-1.95 (m, 4H, $2CH_2$), 1.04 (s, 3H, CH_3), 1.16 (s, 6H, $2CH_3$). ^{13}C NMR δ 213.11 (C=O), 165.34 (2C=N), 142.50 (C), 129.67, 127.05 (4CH), 120.66 (C), 76.66 (C-OH), 58.27(C), 52.84 (CH), 46.20 (C), 27.97, 23.28 ($2CH_2$), 21.92, 21.62, 20.43, 9.45 ($4CH_3$). Anal. Calcd for $C_{19}H_{22}N_2O_3$ (326.16): C 69.92, H 6.79, N 8.58. Found: C 69.86, H 6.73, N 8.52.

3-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4h). White powder, yield 87%, mp 153-155º. IR (KBr): 3354 (OH), 2959, 2925, 1762, 1603, 1542, 1486, 1087, 838 cm^{-1}; ^{1}H NMR δ 7.89 (d, $^3J_{HH}$ = 8.5 Hz, 2H, CH_{arom}), 7.62 (d, $^3J_{HH}$ = 8.5 Hz, 2H, CH_{arom}), 3.78(s, 1H, OH), 2.47 (m, 1H, CH), 1.63-1.97 (m, 4H, $2CH_2$), 1.05 (s, 3H, CH_3), 1.16 (s, 6H, $2CH_3$). ^{13}C NMR δ 210.00 (C=O), 165.73, 153.50 (2C=N), 132.38, 128.49 (4CH), 127.86, 122.21 (2C), 76.23 (C-OH), 58.28 (C), 52.73 (CH), 46.23 (C), 27.95, 23.32 ($2CH_2$), 21.92, 20.43, 9.43 ($3CH_3$). Anal. Calcd for $C_{18}H_{19}BrN_2O_3$ (390.06): C 55.26, H 4.89, N 7.16. Found: C 55.31, H 4.94, N 7.11.

3-[5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4i). Colorless Oil, yield 85%, IR (KBr): 3416 (OH), 2964, 2928, 1760, 1611, 1500, 1417, 1237, 845 cm^{-1}; ^{1}H NMR δ 7.15-8.07(m, 4H, CH_{arom}), 3.55 (s, 1H, OH), 2.51 (m, 1H, CH), 1.74-1.87 (m, 4H, $2CH_2$), 1.05 (s, 3H, CH_3), 1.16 (s, 6H, $2CH_3$). ^{13}C NMR δ 212.96 (C=O), 166.75, 165.26 (2C=N), 161.50 (C, d, $^3J_{CF}$ = 503.3 Hz), 129.44 (2CH, d, $^3J_{CF}$ = 8.8 Hz), 119.87 (C, d, $^4J_{CF}$ = 4.4 Hz), 116.40 (2CH, d, $^2J_{CF}$ = 22.6 Hz), 76.23 (C-OH), 58.28 (C), 52.72 (CH), 46.23 (2C), 27.92, 23.32 ($2CH_2$), 21.91, 20.43, 9.43 ($3CH_3$). Anal. Calcd for $C_{18}H_{19}FN_2O_3$ (330.14): C 65.44, H 5.80, N 8.48. Found: C 65.39, H 5.74, N 8.53.

3-Hydroxyl-1,7,7-trimethyl-3-[5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl]bicyclo[2.2.1]heptan-2-one (4j). White powder, yield 89%, mp 134-136º. IR (KBr): 3282 (OH), 2959, 2927, 1762, 1597, 1557, 1456, 1089, 819, 723, 688 cm^{-1}; ^{1}H NMR δ 7.33-7.83 (m, 4H, CH_{arom}), 3.95 (s, 1H, OH), 2.53 (m, 1H, CH), 2.39 (s, 3H, CH_3), 1.77-1.85 (m, 4H, $2CH_2$), 1.04 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR δ 213.04 (C=O), 165.50 (2C=N), 138.89 (C), 132.72, 128.88, 127.59, 124.26 (4CH), 123.30 (C), 76.66 (C-OH), 58.28 (C), 52.84 (CH), 46.20 (C), 27.97, 23.28 ($2CH_2$), 21.25 (CH_3), 21.93, 20.43, 9.45 ($3CH_3$). Anal.Calcd for $C_{19}H_{22}N_2O_3$ (326.16): C 69.92, H 6.79, N 8.58. Found: C 69.87, H 6.85, N 8.64.

3-Hydroxyl-1,7,7-trimethyl-3-[5-(1-naphthyl)-1,3,4-oxadiazol-2-yl]bicyclo[2.2.1]heptan-2-one (4k). White powder, yield 86%, mp 135-137º. IR (KBr): 3426 (OH), 2925, 2872, 1760, 1579, 1536, 1456, 1108, 857, 774 cm^{-1}; ^{1}H NMR δ 7.51-9.16 (m, 7H, CH_{arom}), 3.62 (s, 1H, OH), 2.57 (m, 1H, CH), 1.66-1.96 (m, 4H, $2CH_2$), 1.08 (s, 3H, CH_3), 1.20 (s, 6H, $2CH_3$). ^{13}C NMR δ 213.34 (C=O), 165.21 (2C=N), 133.86, 130.00, 128.30 (3C), 132.84, 128.74, 128.66, 128.22, 126.71, 126.04, 124.78 (7CH), 76.43 (C-OH), 58.33 (C), 52.87 (CH), 46.28 (C), 28.03, 23.36 ($2CH_2$), 21.95, 20.45, 9.47 ($3CH_3$). Anal. Calcd for $C_{22}H_{22}N_2O_3$ (362.16): C 72.91, H 6.12, N 7.73. Found: C 72.85, H 6.17, N 7.78.

3-[5-(3-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4l). White powder, yield 88%, mp 146-148º. IR (KBr): 3272 (OH), 2962, 2928, 1764, 1581, 1547, 1444, 1092, 806, 779, 680 cm^{-1}; ^{1}H NMR δ 7.43-8.01 (m, 4H, CH_{arom}), 3.15 (s, 1H, OH), 2.52 (m, 1H, CH), 1.70-1.95 (m, 4H, $2CH_2$), 1.05 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). ^{13}C NMR δ 213.12 (C=O), 165.34, 161.20 (2C=N), 135.31 (C), 132.02, 130.22, 127.06, 125.19 (4CH), 124.13 (C), 73.65 (C-OH), 58.46 (C), 52.82 (CH), 46.24 (C), 27.94, 23.31 ($2CH_2$), 21.92, 20.42, 9.43 ($3CH_3$). Anal. Calcd for $C_{18}H_{18}ClN_3O$ (327.81): C 65.95, H 5.53, N 12.82. Found: C 65.83, H 5.49, N 12.77.

3-Hydroxyl-1,7,7-trimethyl-3-[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]bicyclo[2.2.1]heptan-2-one (4m). White powder, yield 87%, mp 110-112º. IR (KBr): 3417 (OH), 2957, 2925, 1763, 1600, 1542, 1455, 1109, 772, 723 cm^{-1}; ^{1}H NMR δ 7.05-7.91 (m, 4H, CH_{arom}), 3.80 (s, 1H, OH), 2.64 (s, 3H, CH_3), 2.48 (m, 1H, CH), 1.69-1.97 (m, 4H, $2CH_2$), 1.04 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR δ 213.95 (C=O), 168.45, 166.35 (2C=N), 138.51 (C), 131.72, 131.44, 129.17, 126.13 (4CH), 122.53 (C), 93.15 (C-OH), 58.31 (C), 52.87 (CH), 46.26 (C), 28.05, 23.25 ($2CH_2$), 19.24 (CH_3), 21.94, 20.41, 9.44 ($3CH_3$). Anal. Calcd for $C_{19}H_{22}N_2O_3$ (326.16): C 69.92, H 6.79, N 8.58. Found: C 69.86, H 6.73, N 8.64.

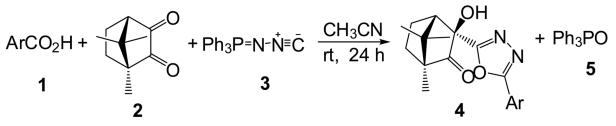
3-Hydroxyl-1,7,7-trimethyl-3-[5-(3-phenoxyphenyl)-1,3,4-oxadiazol-2-yl]bicyclo[2.2.1]heptan-2-one (4n). White powder, yield 86%, mp 105-107°. IR (KBr): 3159 (OH), 2950, 2927, 1762, 1596, 1551, 1448, 1098, 894, 759, 688 cm^{-1}; ^1H NMR δ 7.01-7.77 (m, 9H, CH_{arom}), 3.62 (s, 1H, OH), 2.49 (m, 1H, CH), 1.68-1.96 (m, 4H, $2CH_2$), 1.04 (s, 3H, CH_3), 1.15 (s, 6H, $2CH_3$). ^{13}C NMR δ 205.96 (C=O), 165.97, 157.98 (2C=N), 156.45, 154.60 (2C), 130.53, 129.98, 124.98, 124.01, 121.75, 119.23, 117.07 (9CH), 122.11 (C), 76.45 (C-OH), 58.26 (C), 52.88 (CH), 46.21 (C), 27.90, 23.31 ($2CH_2$), 21.92, 20.42, 9.44 ($3CH_3$). Anal. Calcd for $C_{24}H_{24}N_2O_4$ (404.17): C 71.27, H 5.98, N 6.93. Found: C 71.33, H 5.92, N 6.87.

3-[5-(3,5-Dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4o). Yellow Oil, yield: 88%. IR (KBr): 3465 (OH), 2961, 2873, 1762, 1601, 1557, 1456, 1159, 884 cm^{-1}; ^1H NMR δ 6.58-7.19 (m, 3H, CH_{arom}), 3.82 (s, 6H, OCH_3), 3.70 (s, 1H, OH), 2.51 (m, 1H, CH), 1.67-1.90 (m, 4H, $2CH_2$), 1.03 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR δ 213.87 (C=O), 166.67, 161.07 (2C=N), 161.07, 124.86 (3C), 104.18, 104.62 (3CH), 76.45 (C-OH), 58.28 (C), 55.64 ($2OCH_3$), 52.78 (CH), 46.19 (C), 27.94, 23.29 ($2CH_2$), 21.92, 20.43, 9.44 ($3CH_3$). Anal. Calcd for $C_{20}H_{24}N_2O_5$ (372.17): C 64.50, H 6.50, N 7.52. Found: C 64.45, H 6.55, N 7.57.

Results and Discussion

As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[26-29] we wish to report the synthesis of a disubstituted 1,3,4-oxadiazole derivatives **4** by a three-component condensation of (*N*-isocyanimino)triphenylphosphorane **3**, aromatic carboxylic acid derivatives **1** and (1*R*)-(−)-campherchinon **2** (Scheme 1). The carboxylic acid derivatives **1** with (1*R*)-(−)-campherchinon **2** and (*N*-isocyanimino)-triphenylphosphorane **3** in CH_3CN react together in a 1:1:1 ratio at room temperature to produce sterically congested 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 (Other aspects of these types multicomponent reactions are currently under investigation in our laboratory).

The structures of the products were deduced from their IR, ^1H NMR, ^{13}C NMR, Mass and elemental analyses. For example the ^1H NMR spectrum of **4a** consisted of a two singlet for $3CH_3$ of campherchinon ring (δ 1.05 and 1.16), a multiplet for the $2CH_2$ of campherchinon ring (δ 1.68-1.91), a multiplet for CH of campherchinon ring (δ 2.52) and a



Scheme 1. Three-component synthesis of sterically congested 2,5-disubstituted 1,3,4-oxadiazoles 4 (see Table 1).

Table 1. Synthesis of sterically congested 1,3,4-oxadiazole derivatives **4a-o** from (1*R*)-(−)-campherchinon **2** and (*N*-isocyanimino)-triphenylphosphorane **3** in the presence of carboxylic acid **1** (See Scheme 1)

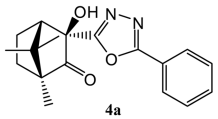
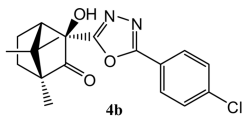
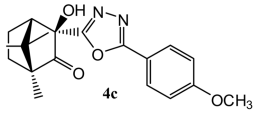
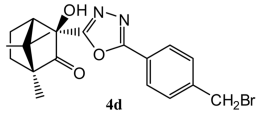
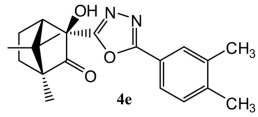
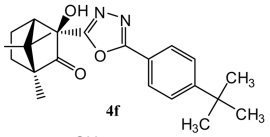
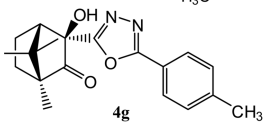
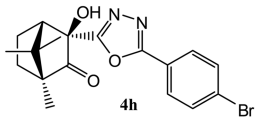
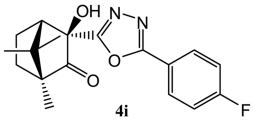
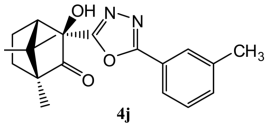
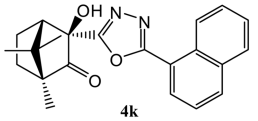
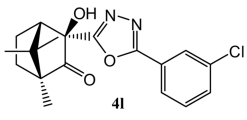
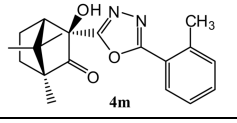
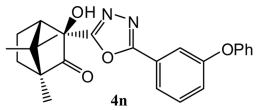
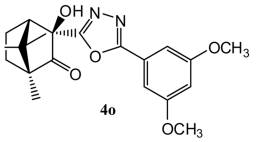
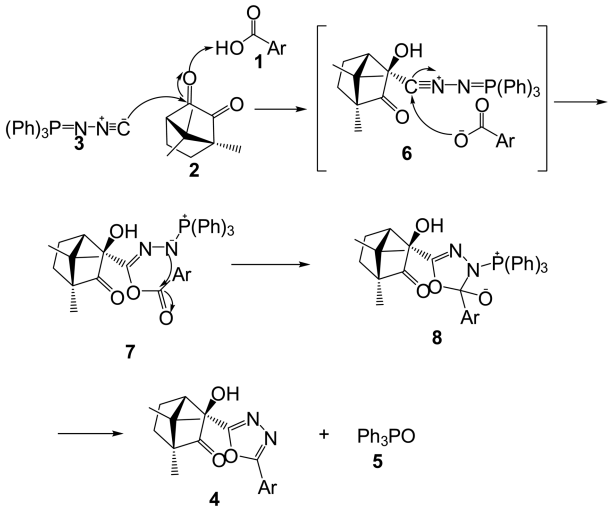
	ArCOOH	Product	Yield[a] (%)
1	C_6H_5COOH	 **4a**	90
2	$4\text{-}ClC_6H_4COOH$	 **4b**	88
3	$4\text{-}MeOC_6H_4COOH$	 **4c**	87
4	$4\text{-}BrCH_2C_6H_4COOH$	 **4d**	88
5	$3,4\text{-}diMeC_6H_4COOH$	 **4e**	86
6	$4\text{-}t\text{-}BuC_6H_4COOH$	 **4f**	87
7	$4\text{-}MeC_6H_4COOH$	 **4g**	86
8	$4\text{-}BrC_6H_4COOH$	 **4h**	87
9	$4\text{-}FC_6H_4COOH$	 **4i**	85
10	$3\text{-}MeC_6H_4COOH$	 **4j**	89
11	$C_{10}H_7COOH$	 **4k**	86
12	$3\text{-}ClC_6H_4COOH$	 **4l**	88
13	$2\text{-}MeC_6H_4COOH$	 **4m**	87

Table 1. Continued

	ArCOOH	Product	Yield[a] (%)
14	3-PhOC$_6$H$_4$COOH	 **4n**	86
15	3,5-diMeOC$_6$H$_3$COOH	 **4o**	88

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



Scheme 2. Proposed mechanism for the formation of sterically congested 2,5-disubstituted 1,3,4-oxadiazole derivatives **4**.

singlet for OH (δ 3.65, exchangeable by D_2O). The aryl groups exhibited characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 16 distinct signals, partial assignment of these signals is given in the experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **4b-o** were similar to those of **4a**, except for the aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

The suggested mechanism for the formation of products **4a-o** is illustrated in Scheme 2. On the basis of the chemistry of isocyanides, it is reasonable to assume that the first step may involve *endo*-selective nucleophilic addition of the (*N*-isocyanimino)triphenylphosphorane **3** to (1*R*)-(−)-camphorchinon **2**, which facilitates by its protonation with the acid **1**, leading to nitrilium intermediate **6**. Due to steric hinderance of C_2 and also exo direction of C_3, nucleophilic attack happens from the endo direction of C_3. Intermediate **6** may be attacked by conjugate base of the acid **1** to form 1:1:1 adduct **7**. This adduct may undergo intramolecular *aza*-Wittig reaction[26-29] 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**.

Conclusions

We believe that the reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazole derivatives **4** from (1*R*)-(−)-camphorchinon, *N*-isocyaniminotriphenylphosphorane **3** and aromatic carboxylic acids. Its ease of workup, high yields and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies.

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