Turk J Chem
36 (2012) , 81 – 91.

doi:10.3906/kim-1107-19

Four-component synthesis of 1,3,4-oxadiazole derivatives from N-isocyaniminotriphenylphosphorane, aromatic carboxylic acids, aromatic bis-aldehydes, and secondary amines

Ali RAMAZANI[1,*], Zahra KARIMI[1], Ali SOULDOZI[2], Yavar AHMADI[3]
[1] *Chemistry Department, Zanjan University, PO Box 45195-313, Zanjan-IRAN*
[2] *Chemistry Department, Urmia Branch, Islamic Azad University, PO Box 969, Urmia-IRAN*
[3] *Young Researchers Club, Zanjan Branch, Islamic Azad University, Zanjan-IRAN*
e-mail: aliramazani@gmail.com

Received: 07.07.2011

The 1:1 iminium intermediate generated by the addition of a secondary amine to aromatic bis-aldehydes (isophthalaldehyde and terphthalaldehyde) is trapped by the N-isocyaniminotriphenylphosphorane in the presence of a aromatic carboxylic acid derivative, which leads to the formation of corresponding iminophosphorane intermediate. Then disubstituted 1,3,4-oxadiazole derivatives are formed via intramolecular *aza*-Wittig reaction of the iminophosphorane intermediates. The reactions were completed in neutral conditions at room temperature and the corresponding disubstituted 1,3,4-oxadiazole derivatives were produced in excellent yields.

Key Words: N-isocyaniminotriphenylphosphorane, aromatic carboxylic acid, aromatic bis-aldehydes, 1,3,4-oxadiazole, *aza*-Wittig reaction, secondary amine

Introduction

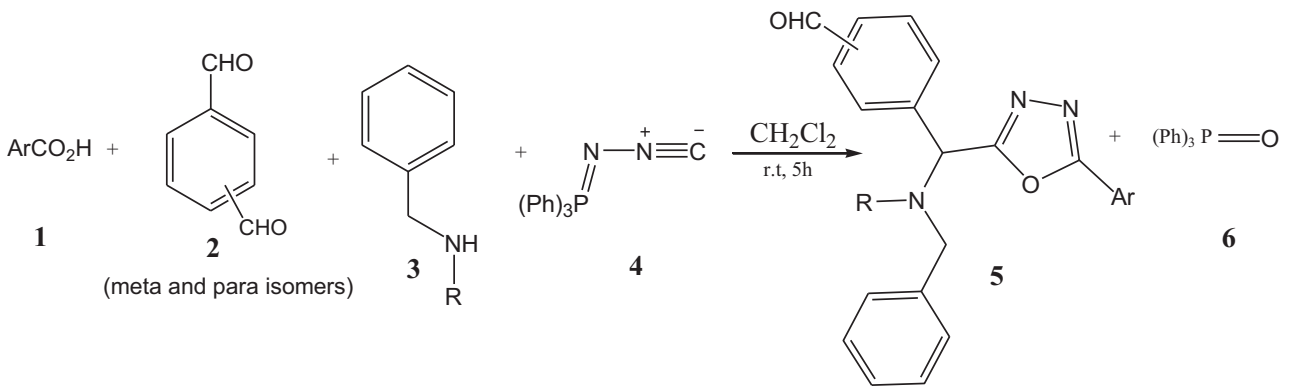
In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase efficiency by combining several operational steps without any isolation of intermediates or changes in the conditions.[1−6] This principle, therefore, is highly efficient in terms of time as well as resources.[7] Among the known multicomponent reactions to date, the most valuable reactions are those

*Corresponding author

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 much attention because of the advantages that they offer to the field of combinatorial chemistry.[8]

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.[9] The proton affinity of these iminophosphoranes can be used as a molecular guide to assess their utility as synthetic reagents and their function as ligands in coordination and organometallic chemistry.[9–17]

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. 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 synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity.[9–20] There are several reports for the use of (*N*-isocyanimino)triphenylphosphorane **4** in the preparation of metal complexes.[16–21] However, the role of *N*-isocyaniminotriphenylphosphorane **4** in organic chemistry remains almost unexplored.[16–21] The *N*-isocyaniminotriphenylphosphorane **4** 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.[20,21] In recent years, we have established a one-pot method for the synthesis of organophosphorus compounds.[18–26] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[27–41] we wish to report the synthesis of a new class of disubstituted 1,3,4-oxadiazole derivatives **5** by a novel 4-component condensation of aromatic carboxylic acids **1,** bis-aldehydes (isophthalaldehyde and terphthalaldehyde) **2**, a secondary amine **3**, and *N*-isocyaniminotriphenylphosphorane **4** in excellent yields under neutral conditions (Scheme 1).



Scheme 1. Four-component synthesis of sterically congested 1,3,4-oxadiazole derivatives **5** (see Table).

1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides.[32–34] They are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, antihypertensive,

analgesic, antibacterial, hypoglycemic, antimalarial, antitubercular and antidepressant.[32–34] Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multi-step in nature.[35–37] The most general method involves the cyclization of diacylhydrazides with a variety of reagents, such as thionyl chloride, phosphorous oxychloride, or sulfuric acid, usually under harsh reaction conditions.[38] A reliable and simple method has been reported by the Ramazani research group for the one-pot synthesis of 1,3,4-oxadiazole derivatives from carboxylic acids and *N*-isocyaniminotriphenylphosphorane **4**[24,31]

Experimental

The 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 were TLC and NMR. TLC and NMR indicated that there was 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}CNMR 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. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Flash chromatography columns were prepared from Merck silica gel powder.

General procedure for the preparation of compounds 5

To a stirred solution of *N*-isocyaniminotriphenylphosphorane **4** (1 mmol), aromatic bis-aldehyde **2** (1 mmol), and secondary amine **3** (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of aromatic carboxylic acids **1** (1 mmol) in CH_2Cl_2 (5 mL) at room temperature over 15 min. The mixture was stirred for 5 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel powder; petroleum ether–ethyl acetate (3:1)). The solvent was removed under reduced pressure and the products were obtained. The characterization data of the compounds are given below:

4–[[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl](dibenzylamino)methyl]benzaldehyde (5a)

Yellow oil, (Yield 90%). IR (neat): ν_{max} = 2980, 1704, 1607, 1482 and 799 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 3.66 and 3.89 (AB quartet, 4H, J = 13.75 Hz, $2CH_2$ of dibenzyl group), 5.50 (s, 1H, CH aliphatic), 7.28-7.92 (m, 18H, H-arom), 10.11 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 54.8 ($2CH_2$ of benzyl group), 59.5 (CH, aliphatic), 127.5, 128.4, 128.5, 128.8, 129.1, 129.9 and 132.5 (18CH of arom), 122.5, 126.7, 136.2, 138.2 and 143.3 (6C of arom), 164.1 and 164.6 (2C=N of oxadiazole), 191.6 (C=O of aldehyde). Anal. Calcd for $C_{30}H_{24}BrN_3O_2$ (538.4): C 66.92, H 4.49, N 7.80; Found: C 66.86, H 4.42, N 7.88. MS, m/z(%): 538 (M^+, 3), 342 (6), 314 (53), 222 (4), 196 (100), 132 (6), 91 (93) and 65 (9).

4–{[Benzyl(ethyl)amino][(5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5b)

Yellow oil, (Yield 84%). IR (neat) ν_{max} = 3035, 2975, 1704, 1610, 1499, 1211 and 827 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.14 (t, 3H, J = 7 Hz, CH_3 of Et), 2.43 (s, 3H, CH_3), 2.50-2.58 and 2.70-2.81 (2m, 2H, CH_2 of Et), 3.58 and 3.90 (AB quartet, 2H, J = 13.75 Hz, CH_2 of benzyl group), 5.49 (s, 1H, CH

aliphatic), 7.22-7.92 (m, 13H, H-arom), 10.01 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.7 and 21.6 ($2CH_3$), 44.6 (CH_2, Ethyl), 54.5 (CH_2 of benzyl group), 60.2 (CH, aliphatic), 126.9, 127.2, 128.4, 128.6, 128.8, 129.7 and 129.8 (13CH of arom), 120.8, 130.1, 136.1, 138.7 and 142.5 (5C of arom), 163.9 and 165.5 (2C=N of oxadiazole), 191.6 (C=O of aldehyde). Anal. Calcd for $C_{26}H_{25}N_3O$ (411.5): C 75.89, H 6.12, N 10.21; Found: C 75.83, H 6.34, N 10.26. MS, m/z(%): 412 (M^+, 29), 278 (56), 252 (68), 235 (6), 159 (12), 134 (100), 119 (34), 77 (13), 65 (11) and 43 (5).

4–{[Benzyl(ethyl)amino][(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5c)

Yellow oil, (Yield 85%). IR (neat) ν_{max} = 3066, 2979, 1705, 1606, 1482 and 740 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.14 (t, 3H, J = 7 Hz, CH_3 of Et), 2.50-2.58 and 2.72-2.77 (2m, 2H, CH_2 of Et), 3.59 and 3.89 (AB quartet, 2H, J = 13.75 Hz, CH_2 of benzyl group), 5.48 (s, 1H, CH aliphatic), 7.21-7.89 (m, 13H, H-arom), 10.01 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.7 (CH_3); 44.7 (CH_2, Ethyl), 54.6 (CH_2 of benzyl group), 60.3 (CH, aliphatic), 127.9, 128.3, 128.4, 128.6, 128.8, 129.9 and 132.4 (13CH of arom), 122.53, 127.2, 136.1, 138.6 and 143.9 (5C of arom), 162.8 and 164.5 (2C=N of oxadiazole), 191.6 (C=O of aldehyde). Anal. Calcd for $C_{25}H_{22}BrN_3O_2$(476.4): C 63.03, H 4.65, N 8.82; Found: C 63.10, H 4.60, N 8.77. MS, m/z(%): 475 (M^+, 15), 463 (34), 448 (18), 436 (59), 430 (26), 278 (79), 235 (6), 160 (6), 134 (100), 119 (18), 91 (41), 65 (6) and 43 (2).

4–{[Benzyl(methyl)amino][(5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5d)

Yellow oil, (Yield 88%). IR (neat) ν_{max} = 2993, 1704, 1613, 1499, 1213 and 828 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.30 and 2.43 (2s, 6H, $2CH_3$), 3.68 (s, 2H, CH_2 of benzyl group), 5.32 (s, 1H, CH aliphatic), 7.29-7.94 (m, 13H, H-arom), 10.02 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.6 and 39.1 ($2CH_3$), 58.9 (CH_2 of benzyl group), 63.7 (CH, aliphatic), 126.9, 127.4, 128.4, 128.8, 129.1, 129.8 and 130.0 (13CH of arom), 120.8, 130.1, 136.1, 138.6 and 142.5 (5C of arom), 163.6 and 166.5 (2C=N of oxadiazole), 191.6 (C=O of aldehyde). Anal. Calcd for $C_{25}H_{23}N_3O_2$ (397.5): C 75.54, H 5.83, N 10.57; Found: C 75.49, H 5.88, N 10.64.

3–{[Benzyl(methyl)amino][(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5e)

Yellow oil, (Yield 83%). IR (neat) ν_{max} = 3088, 2969, 1703, 1604, 1482 and 741 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.27 (s, 3H, CH_3), 3.61 and 3.68 (AB quartet, 2H, $^2J_{HH}$ = 13.5 Hz, CH_2 of benzyl group), 5.29 (s, 1H, CH aliphatic), 7.27-8.04 (m, 13H, H-arom), 10.05 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 39.1 (CH_3), 58.8 (CH_2 of benzyl group), 63.6 (CH, aliphatic), 128.5, 128.7, 128.7, 129.5, 129.7, 130.7 and 132.3 (13CH of arom), 119.5, 127.5, 129.6, 134.3 and 136.8 (5C of arom), 162.8 and 165.0 (2C=N of oxadiazole), 191.8 (C=O of aldehyde). Anal. Calcd for $C_{24}H_{20}BrN_3O_2$ (462.3): C 62.35, H 4.36, N 9.09; Found: C 62.41, H 4.31, N 9.15.

4–{(Dibenzylamino)[5-(4-ethylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5f)

Yellow oil, (Yield 86%). IR (neat) ν_{max} = 3067, 2939, 1705, 1613, 1501 and 753 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.29 (t, J = 7.5 Hz, 3H, CH_3 of Et), 2.74 (q, J = 7.5 Hz, 2H, CH_2 of Et), 3.61 and 3.89 (AB quartet, 4H, J = 13.75 Hz, $2CH_2$ of Benzyl groups), 5.48 (s, 1H, CH aliphatic), 7.28-7.98 (m, 18H, H-arom), 10.03 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 17.0 (CH_3), 28.9 (CH_2, Ethyl), 54.6 ($2CH_2$ of Benzyl groups), 59.8 (CH, aliphatic), 127.1, 127.4, 128.5, 128.6, 128.8, 129.1 and 129.8 (18CH, arom), 126.82, 134.7, 136.1, 138.3 and 141.9 (3C, arom), 163.4 and 167.1 (2C=N of oxadiazole), 191.9 (C=O of aldehyde). Anal. Calcd for $C_{32}H_{29}N_3O_2$ (487.6): C 78.82, H 5.99, N 8.62; Found: C 78.88, H 5.93, N 8.57.

3–{[Benzyl(methyl)amino][(5-(3,5-dimethylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5g)

Yellow oil, (Yield 84%). IR (neat) ν_{max} = 2947, 1707, 1612, 1554, 1456 and 743 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.30 and 2.39 (2s, 9H, $3CH_3$), 3.60 and 3.68 (AB quartet, 2H, J = 13 Hz, CH_2 of benzyl group), 5.32 (s, 1H, CH aliphatic), 7.17-8.08 (m, 12H, H-arom), 10.04 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.2 and 39.0 ($3CH_3$), 58.8 (CH_2 of benzyl group), 63.5 (CH, aliphatic), 124.7, 128.4, 128.8, 129.5, 129.8, 130.79 and 132.3 (12CH of arom), 123.3, 127.4, 133.7, 136.8 and 138.8 (5C of arom), 161.9 and 165.7 (2C=N of oxadiazole), 191.9 (C=O of aldehyde). Anal. Calcd for $C_{26}H_{25}N_3O_2$ (411.5): C 75.89, H 6.12, N 10.21; Found: C 75.81, H 6.19, N 10.25.

4–{[Benzyl(methyl)amino][(5-(2,5-dimethylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5h)

Yellow oil, (Yield 82%). IR (neat) ν_{max} = 2943, 1706, 1614 and 834 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.29, 2.38 and 2.66 (3s, 9H, $3CH_3$), 3.66 (s, 2H, CH_2 of benzyl group), 5.31 (s, 1H, CH aliphatic), 7.11-7.92 (m, 12H, H-arom), 10.01 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.4, 22.0 and 39.2 ($3CH_3$), 58.9 (CH_2 of benzyl group), 63.7 (CH, aliphatic), 119.9, 126.9, 127.4, 128.4, 128.7, 129.0, 130.0 and 132.5 (12CH of arom), 124.4, 127.6, 132.5, 136.2, 138.7 and 142.0 (6C of arom), 163.5 and 164.68 (2C=N of oxadiazole), 191.7 (C=O of aldehyde). Anal. Calcd for $C_{26}H_{25}N_3O_2$ (411.5): C 75.89, H 6.12, N 10.21; Found: C 75.83, H 6.18, N 10.16.

3–{[Benzyl(ethyl)amino][(5-(3,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5i)

Yellow oil, (Yield 86%). IR (neat) ν_{max} = 2977, 1702, 1606, 1495, 1143 and 740 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.13 (t, 3H, CH_3 of Et), 2.33 (s, 6H, $2CH_3$), 2.55 and 2.76 (2q, 2H, CH_2 of Et), 3.58 and 3.90 (AB quartet, 2H, J = 13.75 Hz, CH_2 of Benzyl groups), 5.49 (s, 1H, CH aliphatic), 7.28-8.01 (m, 12H, H-arom), 10.0 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.7, 19.7 and 19.9 ($3CH_3$), 44.5 (CH_2, Ethyl), 54.5 (CH_2 of Benzyl groups), 59.9 (CH); 134.2, 136.6, 137.6, 137.6, 138.1 and 141.2 (6C, arom), 121.1, 124.52, 127.2, 127.9, 128.4, 128.6, 129.1, 129.2, 129.6 and 130.2 (12CH, arom), 164.8 and 165.6 (2C=N of oxadiazole), 191.9 (C=O of aldehyde). Anal. Calcd for $C_{27}H_{27}N_3O_2$ (425.5): C 76.21, H 6.40, N 9.87; Found: C 76.28, H 6.35, N 9.82.

4–{[Benzyl(ethyl)amino][(5-(4-ethylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5j)

Yellow oil, (Yield 83%). IR (neat) ν_{max} = 2971, 1704, 1612, 1501, 1212 and 844 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.11 and 1.27 (2t, J = 7.5 Hz, 6H, CH_3 of Et), 2.52 and 2.69 (2q, J = 7.5 Hz, 4H, CH_2 of Et), 3.57 and 3.91 (AB quartet, 4H, J = 13.75 Hz, $2CH_2$ of Benzyl groups), 5.49 (s, 1H, CH aliphatic), 7.29-8.01 (m, 13H, H-arom), 10.01(s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 12.6 and 15.2 ($2CH_3$), 28.9 and 44.6 ($2CH_2$, Ethyl), 54.5 (CH_2 of Benzyl groups), 60.1 (CH, aliphatic), 121.2, 127.7, 136.1, 140.0 and 148.81 (5C, arom), 127.0, 128.4, 128.6, 128.8, 129.4, 129.9 and 130.1 (13CH, arom), 163.4 and 165.2 (2C=N of oxadiazole); 191.4 (C=O of aldehyde). Anal. Calcd for $C_{27}H_{27}N_3O_2$ (425.5): C 76.21, H 6.40, N 9.87; Found: C 76.26, H 6.37, N 9.91.

3–{[Dibenzylamino][(5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5k)

Yellow oil, (Yield 85%). IR (neat) ν_{max} = 3068, 2951, 1707, 1619, 1498 and 700 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.45 (s, 3H, CH_3), 3.61 and 3.89 (AB quartet, 4H, J = 13.5 Hz, $2CH_2$ of dibenzyl group), 5.48 (s, 1H, CH aliphatic), 7.34-8.01 (m, 18H, H-arom), 10.02 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.6 (CH_3), 54.6 ($2CH_2$ of benzyl group), 59.0 (CH, aliphatic), 126.9, 127.4, 128.5, 128.8, 128.9, 129.3, 129.4, 129.7 and 129.8 (18CH of arom), 121.5, 134.4, 136.5, 138.3, 142.9 (6C of arom), 163.6 and 165.6 (2C=N of oxadiazole), 191.9 (C=O of aldehyde). Anal. Calcd for $C_{31}H_{27}N_3O_2$ (473.6): C 78.62, H 5.75, N 8.87; Found: C 78.57, H 5.79, N 8.83.

3 –{[benzyl(isopropyl)amino][(5-(3,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzaldehyde (5l)

Yellow oil, (Yield 87%). IR (neat) ν_{max} = 2976, 1703, 1611, 1485 and 768 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 0.95 (d, 3H, J = 6.25 Hz, CH_3 amin), 1.17 (d, 3H, J = 6.25 Hz, CH_3 amin), 2.32 (s, 6H, $2CH_3$), 3.15-3.20 (m, 1H, CH amin), 3.82 and 3.91 (AB quartet, 2H, J = 15 Hz, CH_2 of dibenzyl group), 5.51 (s, 1H, CH aliphatic), 7.05-8.03 (m, 12H, H-arom), 9.99 (s, 1H, CHO). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 18.8, 19.2, 19.7 and 19.9 ($4CH_3$), 53.4 (CH_2 of benzyl group), 50.0 and 58.7 (CH, aliphatic), 124.4, 126.8, 127.8, 128.1, 128.3, 129.2, 129.6, 129.9, 130.1 and 131.0 (12CH of arom), 134.2, 134.6, 136.6, 136.98, 137.42 and 141.0 (6C of arom), 161.2 and 163.4 (2C=N of oxadiazole), 191.0 (C=O of aldehyde). Anal. Calcd for $C_{28}H_{29}N_3O_2$ (439.5): C 76.51, H 6.65, N 9.56; Found: C 76.55, H 6.59, N 9.61.

Results and discussion

The 1:1 imine intermediate generated by the addition of secondary amine **3** with bis-aldehydes (isophthalaldehyde and terphthalaldehyde) **2** is trapped by the N-isocyaniminotriphenylphosphorane in the presence of aromatic carboxylic acid derivatives **1**, which leads to the formation of 1,3,4-oxadiazole derivative 5 and triphenylphosphine oxide **6** (Scheme **1** and Table). The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed.

Table. Synthesis of disubstituted 1,3,4-oxadiazole derivatives **5** (See **Scheme 1**).

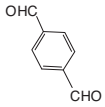
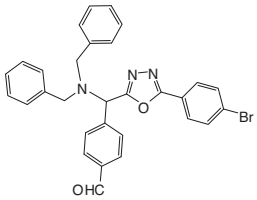
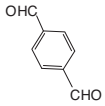
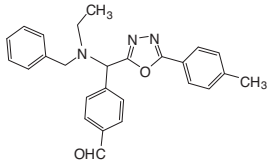
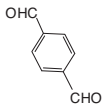
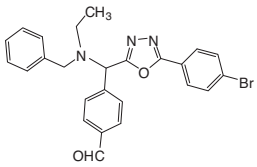
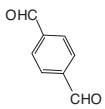
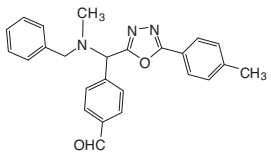
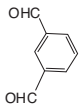
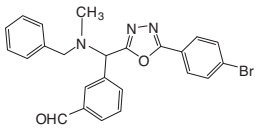
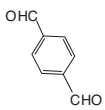
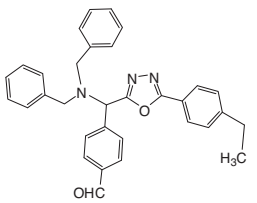
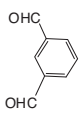
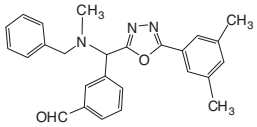
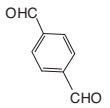
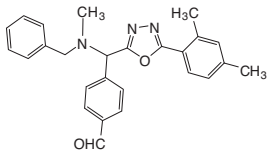
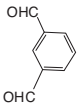
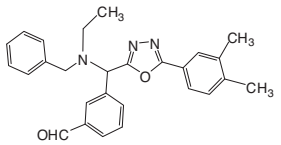
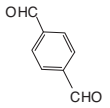
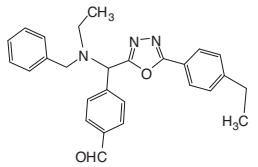
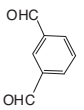
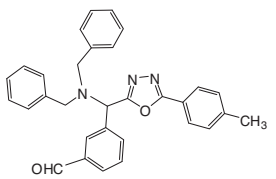
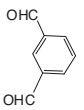
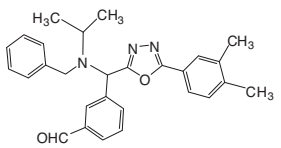
5	Ar	R	Bis-aldehyde	Product	Yield (%)[a]
a	4-BrC_6H_4	C_6H_5			90
b	4-MeC_6H_4	CH_3CH_2			84
c	4-BrC_6H_4	CH_3CH_2			85
d	4-MeC_6H_4	CH_3			88
e	4-BrC_6H_4	CH_3			83
f	4-EtC_6H_4	C_6H_5			86
g	3,5-diMeC_6H_4	CH_3			84

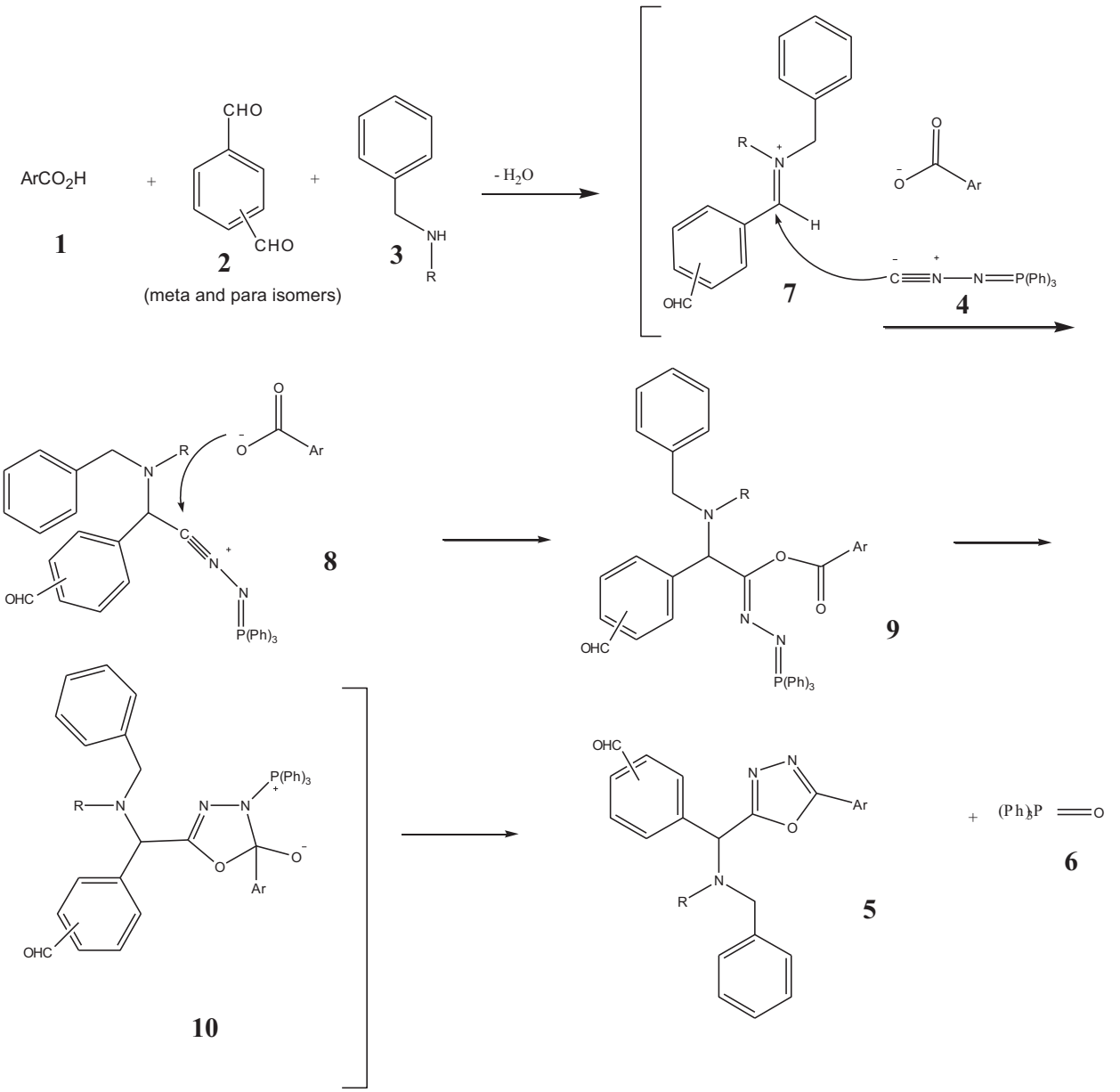
Table. Continued.

5	Ar	R	Bis-aldehyde	Product	Yield (%)[a]
h	2,4-diMeC_6H_4	CH_3			82
i	3,4-diMeC_6H_4	CH_3CH_2			86
j	4-EtC_6H_4	CH_3CH_2			83
k	4-MeC_6H_4	C_6H_5			85
l	3,4-diMeC_6H_4	$(CH_3)CH$			87

[a] Yield of isolated **5**.

The suggested mechanism for this reaction is provided in Scheme 2. It is conceivable that the initial event is the condensation of the bis-aldehyde **2**, secondary amine **3**, and aromatic carboxylic acid **1** entities to an intermediate iminium ion **7**. Nucleophilic addition of the *N*-isocyaniminotriphenylphosphorane **4** to the intermediate iminium ion **7** leads to nitrilium intermediate **8**. This intermediate may be attacked by the conjugate base of the acid **1** to form 1:1:1:1 adduct **9**. This adduct may undergo an intramolecular *aza*-Wittig reaction of an iminophosphorane moiety with the ester carbonyl group to afford the isolated 2,5-disubstituted 1,3,4-oxadiazole **5** by removal of triphenylphosphine oxide **6** from intermediate **10**.

The structures of the products **5a-l** were deduced from their IR, ^{1}HNMR, and ^{13}CNMR spectra. For example the IR spectrum of **5a** showed strong absorptions at 2980 (CH), 1704 (C=O, aldehyde) 1482 (C=C, aromatic) and 799 (aromatic) cm^{-1}. The ^{1}HNMR spectrum of **5a** consisted of an AB-quartet for 2 CH_2 of the benzyl group (δ = 3.66 and 3.89 ppm, J = 13.75 Hz), a singlet for the CH aliphatic (δ = 5.50 ppm), a



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

multiplet for H-Ar (7.28-7.92 ppm), and a singlet for CH of the aldehyde group (δ = 10.11 ppm). The ^{1}H decoupled ^{13}CNMR spectrum of **5a** showed 17 distinct resonances [δ = 54.8 (2 CH_2, benzyl group); 595 (1 CH, aliphatic); 122.5, 126.7, 136.2, 138.2 and 143.3 (6 C, arom.); 127.5, 128.4, 128.5, 128.8, 129.1, 129.9 and 132.5 (18 CH, arom.); 1641 and 1646 (2 C, oxadiazole); 191.6 (1 C=O, aldehyde)] that are in agreement with the formula and structure of **5a**. Partial assignment of these resonances is given in the spectral analysis section (see Experimental section). The ^{1}H and ^{13}CNMR spectra of compounds **5bl** were similar to those of **5a**, except for the aromatic or heteroaromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

Conclusions

In summary, the previously developed method was extended to bis-aldehyde for the preparation of sterically congested 2,5-disubstituted 1,3,4-oxadiazole derivatives **5** from aromatic carboxylic acids **1**, bis-aldehyde **2**, secondary amine **3**, and *N*-isocyaniminotriphenylphosphorane **4** in excellent yields under neutral conditions. Its ease of work-up and reaction conditions make it a useful addition to modern synthetic methodologies. We think that the reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazole derivatives, by a sequence of multicomponent reactions and an intramolecular *aza*-Wittig closure. Due to the easy availability of the synthetic approach and the neutral ring closure conditions, this new synthetic approach discussed here has potential in the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles, which are of considerable interest as potential biologically active compounds or pharmaceuticals. Other aspects of this process are under investigation.

References

1. Kolodiazhnyi, O. I. *Phosphorus Ylides: Chemistry and Application in Organic Synthesis* Wiley, New York 1999
2. a) Ramazani, A.; Kazemizadeh, A. R.; Ahmadi, E.; Noshiranzadeh N.; Souldozi, A. *Curr. Org. Chem.* **2008** *12* 59-82; b) Ramazani, A.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 2663-2666; c) Ramazani, A.; Ahmadi, E. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 2659-2661; d) Ramazani, A.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2004**, *179*, 529-534; e) Ramazani, A.; Bodaghi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2004**, *179*, 1615- 1620; f) Ramazani, A.; Kazemizadeh, A. R.; Ahmadi, E. *Phosphorus, Sulfur, Silicon Relat.Elem.* **2005**, *180*, 1781-1784; g) Ramazani, A.; Azizian, A.; Bandpey, M.; Noshiranzadeh, N. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2006**, *181*, 2731-2734; h) Ramazani, A.; Ahmadi, E. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2006**, *181*, 2725- 2729.
3. a) Ramazani, A.; Kazemizadeh, A. R.; Ahmadi, E.; Slepokura, K.; Lis, T. *Z. Naturforsch.* **2006** *61b*, 1128-1133; b) Ramazani, A.; Noshiranzadeh, N.; Ghamkhari, A.; lepokura, K.; Lis, T. *Helv. Chim. Acta* **2008**, *91*, 2252-2261.
4. Corbridge, D. E. C. *Phosphorus: an Outline of Its Chemistry, Biochemistry, and Uses* 5th ed.; Elsevier, Amsterdam 1995
5. Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197-1218
6. Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2009** *13*, 810-828
7. Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2006**, *10*, 2371-2392
8. Hajós, G.; Nagy, I. *Curr. Org. Chem.* **2008**, *12*, 39-58
9. Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523-575
10. Cossio, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839-2847
11. Palacios, F.; Herrán, E.; Alonso, C.; Rubiales, G.; Lecea, B.; Ayerbe, M.; Cossío, F. P. *J. Org. Chem.* **2006**, *71*, 6020-6030
12. Stolzenberg, H.; Weinberger, B.; Fehlhammer, W. P.; Pühlhofer, F. G.; Weiss, R. *Eur. J. Inorg. Chem.* **2005**, *21*, 4263-4271.
13. Chiu, T. W.; Liu, Y. H.; Chi, K. M.; Wen, Y. S.; Lu, K. L. *Inorg Chem* **2005**, *44*, 6425-6430.

14. Ramazani, A.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 1325-1328.
15. Ramazani, A.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 1329-1332.
16. Ramazani, A.; Bodaghi, A. *Tetrahedron Lett.* **2000**, *41*, 567-568
17. Pakravan, P.; Ramazani, A.; Noshiranzadeh, N.; Sedrpoushan, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2007**, *182*, 545-549
18. Ramazani, A.; Rahimifard, M.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2007**, *182*, 1-5.
19. Ramazani, A.; Rahimifard, M.; Noshiranzadeh, N.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2007**, *182*, 413-417
20. Ramazani, A.; Ahmadi, E.; Kazemizadeh, A. R.; Dolatyari, L.; Noshiranzadeh, N.; Eskandari, I.; Souldozi, A. *Phosphorus, Sulphur, Silicon Relat. Elem* **2005**, *180*, 2419-2422
21. Ramazani, A.; Mohammadi-Vala, M. A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2001**, *176*, 223-229
22. Ramazani, A.; Amini, I.; Massoudi, A. *Phosphorus, Sulphur, Silicon Relat. Elem* **2006**, *181*, 2225-2229
23. a) Souldozi, A.; Ramazani, A.; Bouslimani, N.; Welter, R. *Tetrahedron Lett.* **2007** *48*, 2617-2620; b) Ramazani, A.; Rouhani, M.; Rezaei, A.; Shajari, N.; Souldozi, A. *Helv. Chim. Acta* **2011**, *94*, 282-288; c) Ramazani, A.; Shajari, N.; Mahyari, A.; Ahmadi, Y. *Mol. Divers.* **2011**, *15*, 521-527; d) Nasrabadi, F. Z.; Ramazani, A.; Ahmadi, Y. *Mol. Divers.* **2011**, *15*, 791-798; e) Shajari, N.; Ramazani, A.; Ahmadi, Y. *Bull. Chem. Soc. Ethiop.* **2011**, *25*, 1-6; f) Ramazani, A.; Nasrabadi, F. Z.; Karimi, Z.; Rouhani, M. *Bull. Korean Chem. Soc.* **2011**, *32*, 2700-2704; g) Ramazani, A.; Farshadi, A.; Mahyari, A.; lepokura, K.; Lis, T.; Rouhani, M.; *J. Chem. Crystallogr.* **2011***, 41,* 13761385
24. a) Souldozi, A.; Ramazani, A. *Tetrahedron Lett.* **2007**, *48*, 1549-1551; b) Ramazani, A.; Nasrabadi, F. Z.; Mashhadi Malekzadeh, A.; Ahmadi, Y. *Monatsh. Chem.* **2011**, *142*, 625-630
25. a) Souldozi, A.; Ramazani, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2009** *184*, 3191-3198; b) Ramazani, A.; Ahmadi, Y.; Rouhani, M.; Shajari, N.; Souldozi, A. *Heteroatom Chem.* **2010**, *21*, 368-372
26. a) Souldozi, A.; Ramazani, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2009** *184*, 2344-2350; b) Ramazani, A.; Ahmadi, Y.; Tarasi, R. *Heteroatom Chem.* **2011**, *22* 79-84.
27. Souldozi, A.; Ramazani, A. *Arkivoc* **2008**, *xvi*, 235-242.
28. Ramazani, A.; Salmanpour, S.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2010**, *185*, 97-102
29. Souldozi, A.; lepokura, K.; Lis, T.; Ramazani, A. *Z. Naturforsch.* **2007**, *62b*, 835-840.
30. Ramazani, A.; Morsali, A.; Ganjeie, B.; Kazemizadeh, A. R.; Ahmadi, E.; Kempe, R.; Hertle, I. *Z. Naturforsch.* **2005**, *60b*, 569-571.
31. Ramazani, A.; Rezaei, A. *Org. Lett.* **2010**, *12* 2852-2855.
32. Holla, B. S.; Gonsalves, R.; Shenoy, S. *Eur. J. Med. Chem.* **2000**, *35*, 267-271.
33. Chen, Q.; Zhu, X. –H.; Jiang, L. –L.; Liu, Z. –M.; Yang, G. –F. *Eur. J. Med. Chem.* **2008**, *43*, 595-603
34. Amir, M.; Shikha, K. *Eur. J. Med. Chem.* **2004**, *39*, 535-545
35. Baxendale, I. R.; Ley, S. V.; Martinelli, M. *Tetrahedron* **2005**, *61*, 5323-5349
36. 36 Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett.* **2004**, *45*, 3257-3260
37. Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275 3278.
38. Wang, Y.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 105-108
39. Ramazani, A.; Nasrabadi, F. Z.; Ahmadi, Y. *Helv. Chim. Acta* **2011**, *94*, 1024-1029.
40. Ramazani, A.; Ahmadi, Y.; Nasrabadi, F. Z. *Z. Naturforsch* **2011**, *66b*, 184190
41. Ramazani, A.; Ahmadi, Y.; Mahyari, A. *Synthetic Commun.* **2011**, *41*, 2273- 2282.