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A one-pot efficient four-component reaction for the synthesis of 2-(arylamino)-2-(5-aryl-1-ethenyl-1,3,4-oxadiazol-2-yl)propyl benzoate (or 4-bromobenzoate) derivatives

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Reactions of *N*-isocyaniminotriphenylphosphorane with 2-oxopropyl benzoate (or 2-oxopropyl 4-bromobenzoate) in the presence of 3-phenyl-2-propynoic acid and primary amines proceeded smoothly at room temperature and in neutral conditions to afford sterically congested 1,3,4-oxadiazole derivatives in high yields. The reaction proceeded smoothly and cleanly under mild conditions and no side reactions were observed.

Key Words: 2-Oxopropyl benzoate, 2-oxopropyl 4-bromobenzoate, 3-phenyl-2-propynoic acid, 1,3,4-oxadiazole, *N*-isocyaniminotriphenylphosphorane

Introduction

A multicomponent reaction (MCR) is a chemical reaction in which 3 or more compounds react to form a single product. By definition, MCRs are those reactions whereby more than 2 reactants combine in a sequential manner to give highly selective products that retain the majority of the atoms of the starting material. The development

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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 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 2 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 multicomponent reaction (MCR) chemistry, in which 3 or more starting materials are brought together in a highly convergent approach to rapidly build up molecular structure and complexity.[4]

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, antiinflammatory, and antihypertensive.[5–9]

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multi-step 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] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[22–36] we wish to report the synthesis of sterically congested 2,5-disubstituted 1,3,4-oxadiazoles **7** by a multicomponent reaction between (*N*-isocyanimino)triphenylphosphorane **6**, various primary amines **5**, electron-poor ketones **3** (2-oxopropyl benzoate and 2-oxopropyl 4-bromobenzoate), and 3-phenyl-2-propynoic acid **4**, followed by aza-Wittig cyclization in CH_2Cl_2 at ambient temperature in excellent yields (Scheme 1 and Figure and Table).

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. 2-Oxopropyl benzoate (or 4-bromobenzoate) **3**[38] and *N*-isocyaniminotriphenylphosphorane **6**[12,13] were prepared based on known procedures.

General procedure for the preparation of compounds 7

A mixture of (*N*-isocyanimino)triphenylphosphorane **6** (1 mmol), (2-oxopropyl benzoate and 2-oxopropyl 4-bromobenzoate) **3** (1 mmol), and primary amine **5** (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of 3-phenyl-2-propynoic acid **4** (1 mmol) in CH_2Cl_2 (5 mL) at room temperature over 15 min. The mixture was stirred for 6 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:

2-(benzylamino)-2-[5-(2-phenyl-1-ethynyl)-1,3,4-oxadiazol-2-yl]propyl benzoate (7a)

Yellow oil, (Yield 82%). IR (neat): ν_{max} = 3350 (NH), 2920 (C-H), 2230 (C≡C), 1723 (C=O), 1453 (C=C, aromatic), 1265 (C-O) and 708 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.79 (s, 3H, CH_3), 2.24 (s, 1H, NH), 3.77 and 3.83 (AB quartet, 2H, J = 12.50 Hz, CH_2 of benzyl group), 4.58 and 4.68 (AB quartet, J = 11.0 Hz, 2H, CH_2 aliphatic), 7.27-7.99 (m, 15 H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.9 (CH_3), 47.7 (CH_2 of benzyl group), 56.9 (C aliphatic), 69.0 (CH_2 aliphatic), 72.8 and 97.2 (2 C, acetylene), 119.6, 129.4 and 139.5 (3 C, arom.), 127.2, 128.1, 128.4, 128.5, 128.7, 129.7, 130.1, 132.5 and 133.3 (15 CH, arom.), 151.6 and 165.8 (2C of oxadiazole), 168.6 (C of benzoate group). Analysis of $C_{27}H_{23}N_3O_3$ (437.50): calcd. C 74.12, H 5.30, N 9.60; found C 74.16, H 5.25, N 9.63. MS, m/z(%): 438 (M^+, 1.85), 392 (2), 332 (3), 302 (33), 284 (18), 211 (30), 179 (70), 148 (100), 135 (89), 114 (64), 91 (63), 77 (98), 51 (57).

2-[(4-methoxybenzyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl]propyl benzoate (7b)

Yellow oil, (Yield 79%). IR (neat): ν_{max} = 3431 (NH), 2930 (C-H), 2233 (C≡C), 1723 (C=O), 1451 (C=C, aromatic), 1265 (C-O) and 710 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm):1.78 (s, 3H, CH_3), 2.24 (s, 1H, NH), 3.69 and 3.75 (AB quartet, 2H, J = 12.0 Hz, CH_2 of benzyl group), 3.77 (s, 3H, OCH_3), 4.57 and 4.66 (AB quartet, J = 11.0 Hz, 2H, CH_2 aliphatic), 6.84 (d, J = 8.50 Hz, 2H, CH-Ar), 7.24-7.64 (m, 10 H, arom.), 7.97 (d, J = 7.25 Hz, 2H, CH-Ar). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.9 (CH_3), 47.1 (CH_2 of benzyl group), 55.2 (OCH_3), 56.8 (C aliphatic), 69.0 (CH_2 aliphatic), 72.8 and 96.8 (2 C, acetylene), 119.6, 129.5, 131.5 and 158.8 (4 C, arom.), 113.9, 128.4, 128.6, 129.3, 129.6, 130.7, 132.3 and 133.3 (14 CH, arom.), 151.3 and 165.8 (2C of oxadiazole), 168.7 (C of benzoate group). Analysis of $C_{28}H_{25}N_3O_4$ (467.50): calcd. C 71.93, H 5.39, N 8.99; found C 71.87, H 5.42, N 9.02. MS, m/z(%): 468 (M^+, 59), 333 (3), 291 (51), 211 (7), 136 (35), 121 (100), 105 (92), 91 (9), 77 (42).

2-[(4-methylbenzyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl}propyl benzoate (7c)

Yellow oil, (Yield 75%). IR (neat): ν_{max} = 3425 (NH), 2924 (C-H), 2231 (C≡C), 1723 (C=O), 1450 (C=C, aromatic), 1268 (C-O) and 710 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.77 and 2.30 (s, 6H, $2CH_3$), 2.23 (s, 1H, NH), 3.70 and 3.77 (AB quartet, 2H, J = 12.50 Hz, CH_2 of benzyl group), 4.56 and 4.66 (AB quartet, J = 11.0 Hz, 2H, CH_2 aliphatic), 7.10 (d, J = 7.75 Hz, 2H, CH-Ar), 7.21 (d, J = 7.75 Hz, 2H, CH-Ar), 7.31-8.10 (m, 10 H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.8 and 21.0 (2 CH_3), 47.4

(CH_2 of benzyl group), 56.8 (C aliphatic), 69.0 (CH_2 aliphatic), 72.8 and 97.1 (2 C, acetylene), 119.6, 129.8, 136.4 and 136.9 (4 C, arom.), 128.1, 128.4, 128.6, 129.1, 129.6, 130.7, 132.3 and 133.3 (14 CH, arom.), 154.5 and 165.8 (2C of oxadiazole), 168.7 (C of benzoate group). Analysis of $C_{28}H_{25}N_3O_3$ (451.50): calcd. C 74.48, H 5.58, N 9.31; found C 74.52, H 5.53, N 9.34. MS, m/z(%): 451 (M^+, 64), 387 (7), 317 (14), 276 (68), 210 (5), 129 (6), 120 (20), 105 (100), 77 (32).

2-[(4-methylbenzyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl}propyl 4-bromobenzoate (7d)

Yellow oil, (Yield 73%). IR (neat): ν_{max} = 3445 (NH), 2922 (C-H), 2230 (C≡C), 1722 (C=O), 1538 (C=C, aromatic), 1264 (C-O) and 753 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.77 and 2.31 (s, 6H, $2CH_3$), 2.23 (s, 1H, NH), 3.70 and 3.77 (AB quartet, 2H, J = 12.25 Hz, CH_2 of benzyl group), 4.55 and 4.66 (AB quartet, J = 11.0 Hz, 2H, CH_2 aliphatic), 7.10-7.63 (m, 11H, arom.), 7.82 (d, J = 7.25 Hz, 2H, CH-Ar). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.8 and 21.0 (2 CH_3), 47.4 (CH_2 of benzyl group), 56.8 (C aliphatic), 69.2 (CH_2 aliphatic), 72.7 and 97.1 (2 C, acetylene), 119.6, 129.3, 129.5, 136.3 and 136.9 (5 C, arom.), 128.1, 128.5, 129.2, 130.7, 131.1, 131.8 and 132.3 (13 CH, arom.), 151.7 and 165.1 (2C of oxadiazole), 168.5 (C of benzoate group). Analysis of $C_{28}H_{24}BrN_3O_3$ (530.4): calcd. C 63.40, H 4.56, N 7.92; found C 63.46, H 4.52, N 7.97.

2-[(2-chlorobenzyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl]propyl benzoate (7e)

Yellow oil, (Yield 72%). IR (neat): ν_{max} = 3432 (NH), 2926 (C-H), 2231 (C≡C), 1724 (C=O), 1540 (C=C, aromatic), 1269 (C-O), 710 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.81 (s, 3H, CH_3), 2.24 (s, 1H, NH), 3.90 (s, 2H, CH_2 of benzyl group), 4.60 and 4.70 (AB quartet, J = 10.75 Hz, 2H, CH_2 aliphatic), 7.19-8.11 (m, 14 H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.7 (CH_3), 45.1 (CH_2 of benzyl group), 56.7 (C aliphatic), 68.8 (CH_2 aliphatic), 72.7 and 97.1 (2 C, acetylene), 119.7, 129.4, 129.8 and 133.6 (4 C, arom.), 127.0, 128.4, 128.6, 129.5, 129.7, 130.2, 130.6, 132.3, 133.3 and 136.8 (14 CH, arom.), 151.3 and 165.7 (2C of oxadiazole), 168.4 (C of benzoate group). Analysis of $C_{27}H_{22}ClN_3O_3$ (471.9): calcd. C 68.71, H 4.70, N 8.90; found C 68.77, H 4.65, N 8.94.

2-[(2-furylmethyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl]propyl 4-bromobenzoate (7f)

Yellow oil, (Yield 78%). IR (neat): ν_{max} = 3341 (NH), 2926 (C-H), 2231 (C≡C), 1724 (C=O), 1590 (C=C, aromatic) and 754 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.76 (s, 3H, CH_3), 2.24 (s, 1H, NH), 3.84 (s, 2H, CH_2 of benzyl group), 4.52 and 4.63 (AB quartet, J = 11.0 Hz, 2H, CH_2 aliphatic), 6.13 and 6.27 (s, 2H, CH of furyl), 7.25-7.84 (m, 10H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.6 (CH_3), 40.4 (CH_2 of benzyl group), 56.3 (C aliphatic), 69.1 (CH_2 aliphatic), 72.8 and 96.7 (2 C, acetylene), 119.7, 128.5 , 130.7 and 131.9 (4 C, arom.), 107.2, 110.3, 128.6, 128.7, 131.1, 131.8, 132.3 and 142.0 (12 CH, arom.), 152.6 and 165.7 (2C of oxadiazole), 168.2 (C of benzoate group). Analysis of $C_{25}H_{20}BrN_3O_4$ (506.3): calcd. C 59.30, H 3.98, N 8.30; found C 59.27, H 4.02, N 8.25.

2-[(2-methoxybenzyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl]propyl 4-bromobenzoate (7g)

Yellow oil, (Yield 70%). IR (neat): ν_{max} = 3340 (NH), 2939 (C-H), 2231 (C≡C), 1724 (C=O), 1538 (C=C, aromatic), 1269 (C-O) and 711 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.80 (s, 3H, CH_3), 2.22 (s, 1H, NH), 3.77 (s, 2H, CH_2 of benzyl group), 3.79 (s, 3H, OCH_3), 4.61 (s, 2H, CH_2 aliphatic), 6.79-7.93 (m, 13 H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.5 (CH_3), 43.2 (CH_2 of benzyl group), 55.1 (OCH_3), 56.4 (C aliphatic), 69.1 (CH_2 aliphatic), 72.9 and 96.9 (2 C, acetylene), 119.7, 127.1, 131.5, 131.8 and 157.3 (5 C, arom.), 110.2, 120.6, 128.4, 128.7, 129.8, 130.6, 131.1, 131.8 and 132.2 (13 CH, arom.), 151.1 and 165.0 (2C of oxadiazole), 168.6 (C of benzoate group). Analysis of $C_{28}H_{24}BrN_3O_4$ (546.4): calcd. C 61.55, H 4.43, N 7.69; found C 61.58, H 4.37, N 7.73.

2-[(2-methoxybenzyl)amino]-2-[5-(2-phenyl-1-ethyenyl]-1,3,4-oxadiazol-2-yl]propyl benzoate (7h)

Yellow oil, (Yield 71%). IR (neat): ν_{max} = 3433 (NH), 2930 (C-H), 2231 (C≡C), 1724 (C=O), 1569 (C=C, aromatic), 1267 (C-O) and 709 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.82 (s, 3H, CH_3), 2.25 (s, 1H, NH), 3.74 and 3.81 (AB quartet, 2H, J = 12.37 Hz, CH_2 of benzyl group), 3.79 (s, 3H, OCH_3), 4.57 and 4.64 (AB quartet, J = 11.25 Hz, 2H, CH_2 aliphatic), 6.79-8.0 (m, 14 H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.5 (CH_3), 43.3 (CH_2 of benzyl group), 55.1 (OCH_3), 56.5 (C aliphatic), 68.96 (CH_2 aliphatic), 72.9 and 96.9 (2 C, acetylene), 119.7, 127.2, 129.5 and 157.3 (4 C, arom.), 110.2, 120.6, 128.4, 128.7, 129.1, 129.6, 129.8, 130.6, 132.2 and 133.2 (14 CH, arom.), 151.1 and 165.7 (2C of oxadiazole), 168.7 (C of benzoate group). Analysis of $C_{28}H_{25}N_3O_4$ (467.5): calcd. C 71.93, H 5.39, N 8.99; found C 71.88, H 5.42, N 8.95.

2-[(2-furylmethyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl]propyl benzoate (7i)

Yellow oil, (Yield 77%). IR (neat): ν_{max} = 3433 (NH), 2925 (C-H), 2231 (C≡C), 1724 (C=O), 1450 (C=C, aromatic), 1269 (C-O) and 711 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.78 (s, 3H, CH_3), 2.24 (s, 1H, NH), 3.85 (s, 2H, CH_2 of benzyl group), 4.55 and 4.65 (AB quartet, J = 11.50 Hz, 2H, CH_2 aliphatic), 6.13-6.27 (m, 2H, CH of furyl), 7.32-7.99 (m, 11H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.6 (CH_3), 40.4 (CH_2 of benzyl group), 56.4 (C aliphatic), 68.9 (CH_2 aliphatic), 119.7, 129.3 and 152.7 (3 C, arom.), 107.1, 110.3, 128.4, 128.6, 129.6, 130.6, 132.3, 133.3 and 142.0 (13 CH, arom.), 151.3 and 165.7 (2C of oxadiazole), 168.3 (C of benzoate group). Analysis of $C_{25}H_{21}N_3O_4$ (427.50): calcd. C 70.25, H 4.95, N 9.83; found C 70.28, H 4.91, N 9.89.

2-[(4-methoxybenzyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl]propyl 4-bromobenzoate (7j)

Yellow oil, (Yield 78%). IR (neat): ν_{max} = 3434 (NH), 2931 (C-H), 2230 (C≡C), 1724 (C=O), 1590 (C=C, aromatic), 1267 (C-O) and 755 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.77 (s, 3H, CH_3), 2.24 (s, 1H, NH), 3.69 and 3.73 (AB quartet, 2H, J = 11.50 Hz, CH_2 of benzyl group), 3.77 (s, 3H, OCH_3), 4.56 and 4.67 (AB quartet, J = 11.25 Hz, 2H, CH_2 aliphatic), 6.84 (d, J = 8.5 Hz, 2H, CH-Ar), 7.23-7.64

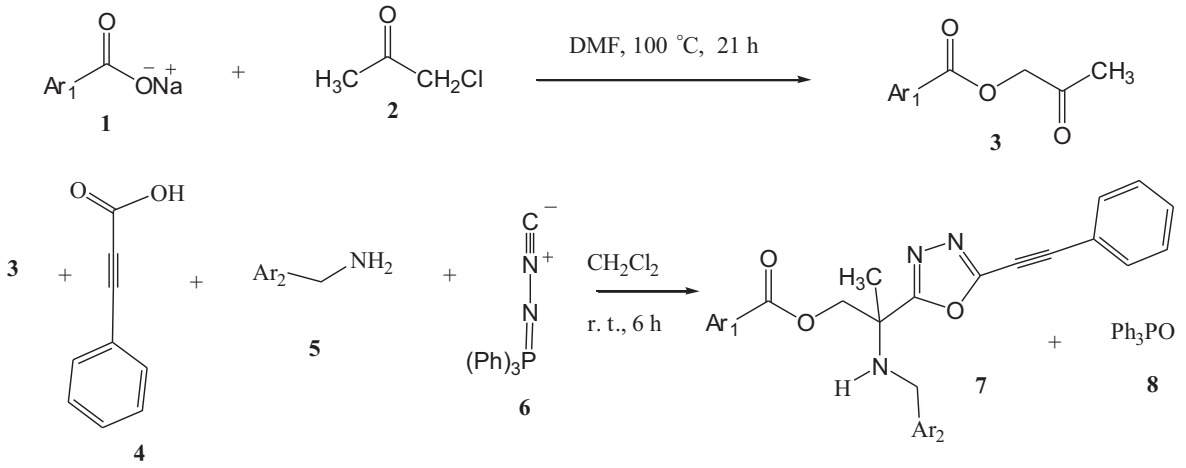
(m, 9 H, arom.), 7.82 (d, J = 8.5 Hz, 2H, CH-Ar). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 20.8 (CH_3), 47.1 (CH_2 of benzyl group), 55.2 (OCH_3), 56.8 (C aliphatic), 69.1 (CH_2 aliphatic), 72.8 and 96.8 (2 C, acetylene), 119.7, 129.4, 130.7, 132.4 and 158.8 (5 C, arom.), 113.9, 128.1, 129.4, 131.1, 131.2, 131.8 and 132.3 (13 CH, arom.), 151.4 and 165.8 (2C of oxadiazole), 168.7 (C of benzoate group). Analysis of $C_{28}H_{24}BrN_3O_4$ (546.40): calcd. C 61.55, H 4.43, N 7.69; found C 61.51, H 4.46, N 7.67.

2-[(1-naphthylmethyl)amino]-2-[5-(2-phenyl-1-ethynyl]-1,3,4-oxadiazol-2-yl]propyl benzoate (7k)

Yellow oil, (Yield 70%). IR (neat): ν_{max} = 3435 (N-H), 2921 (C-H), 2241 (C≡C), 1723 (C=O), 1450 (C=C, aromatic), 1281 (C-O) and 711 (aromatic) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.88 (s, 3H, CH_3), 2.23 (s, 1H, NH), 4.21 and 4.27 (AB quartet, 2H, J = 12.25 Hz, CH_2 of benzyl group), 4.63 and 4.76 (AB quartet, J = 10.75 Hz, 2H, CH_2 aliphatic), 7.41-8.14 (m, 17 H, arom.). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.0 (CH_3), 45.5 (CH_2 of benzyl group), 57.0 (C aliphatic), 68.8 (CH_2 aliphatic), 72.8 and 97.2 (2 C, acetylene), 119.7, 129.4, 131.7, 133.8 and 134.9 (5 C, arom.), 123.7, 125.4, 125.7, 126.2, 126.6, 128.2, 128.4, 128.7, 129.7, 130.7, 132.3 and 133.3 (17 CH, arom.), 151.4 and 165.8 (2C of oxadiazole), 168.6 (C of benzoate group). Analysis of $C_{31}H_{25}N_3O_3$ (487.5): calcd. C 76.37, H 5.17, N 8.62; found C 76.40, H 5.22, N 8.68.

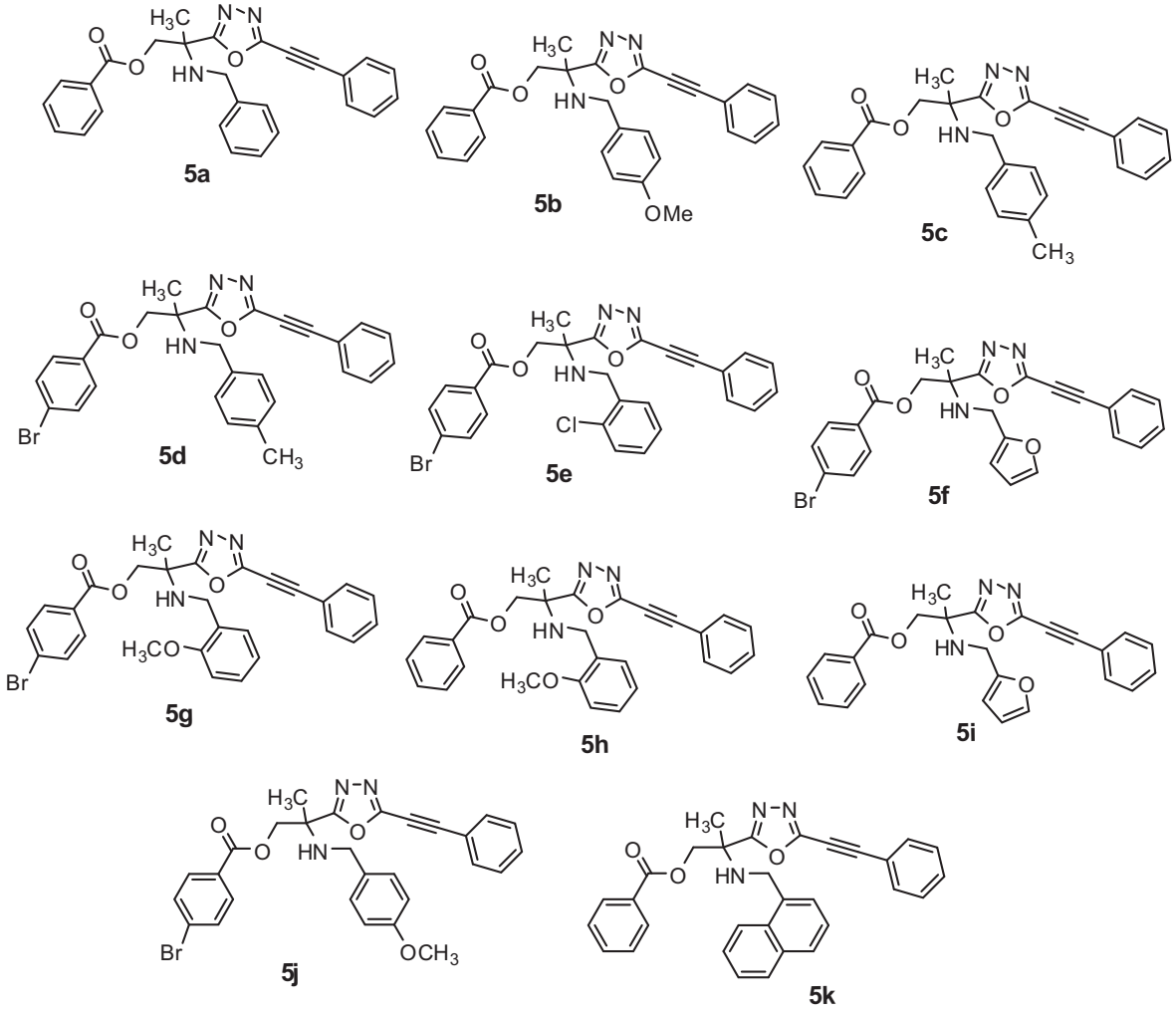
Results and discussion

Recently, 1,3,4-oxadiazoles have been the object of intense research in organic synthesis and medicinal chemistry, and several procedures have been reported for the synthesis of these heterocyclic compounds, which are multi-step in nature.[22] Accordingly, development of a synthetic procedure that could be used to prepare a diversity of these templates remains a significant task. Over the last few years, several synthetic methods have been reported for the preparation of $N-$isocyaniminotriphenylphosphorane ($CNNPPh_3$) **6**.[12,13] There are several reports on the use of N-isocyaniminotriphenylphosphorane ($CNNPPh_3$) **6** in the synthesis of metal complexes.[12,13]



Scheme 1. Synthesis of 2-oxopropyl benzoate (or 2-oxopropyl 4-bromobenzoate) and 4-component synthesis of disubstituted 1,3,4-oxadiazole derivatives **7a-k** (see Figure and Table and Text).

However, application of **6** in the synthesis of organic compounds is fairly rare.[28−37] In recent years, we have established a one-pot method for the synthesis of organophosphorus compounds.[14−21,37] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[22−36] we wish to report the synthesis of sterically congested 2,5-disubstituted 1,3,4-oxadiazoles **7** by a multicomponent reaction between (*N*-isocyanimino)triphenylphosphorane **6**, various primary amines **5**, electron-poor ketones **3** (2-oxopropyl benzoate and 2-oxopropyl 4-bromobenzoate), and 3-phenyl-2-propynoic acid **4**, followed by aza-Wittig cyclization in CH_2Cl_2 at ambient temperature in excellent yields (Scheme 1 and Figure and Table).



Product	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k
Yield (%)	82	79	75	73	72	78	70	71	77	78	70

Figure. Four-component synthesis of disubstituted 1,3,4-oxadiazole derivatives **7a-k** (see Table and Text).

A mechanistic rationalization for this reaction is provided in Scheme 2. It is conceivable that the initial event is the condensation reaction of the 3-phenyl-2-propynoic acid **4**, 2-oxopropyl benzoate (or 4-bromobenzoate) **3**, and primary amine **5** that leads to an intermediate iminium ion **9**. Nucleophilic addition of

the *N*-isocyaniminotriphenylphosphorane **6** to the intermediate iminium ion **9** leads to nitrilium intermediate **10**. This intermediate may be attacked by the conjugate base of the acid **4** to form 1:1:1 adduct **11**. This adduct may undergo an intramolecular aza-Wittig reaction of an iminophosphorane moiety with the ester carbonyl group to afford the isolated disubstituted 1,3,4-oxadiazole **7** by removal of triphenylphosphine oxide **8** from intermediate **12**. We also used acetone and acetophenone instead of electron-poor ketones **3** (2-oxopropyl benzoate and 2-oxopropyl 4-bromobenzoate) **2** in this reaction, but no corresponding products **7** were observed, and the acetone and acetophenone were recovered unreacted at the end of the reaction. As indicated in the Table, the reactions proceeded efficiently with an electron-poor ketone **3** and electron-rich ketones such as acetone and acetophenone are not suitable starting materials in these reactions (Scheme 1).

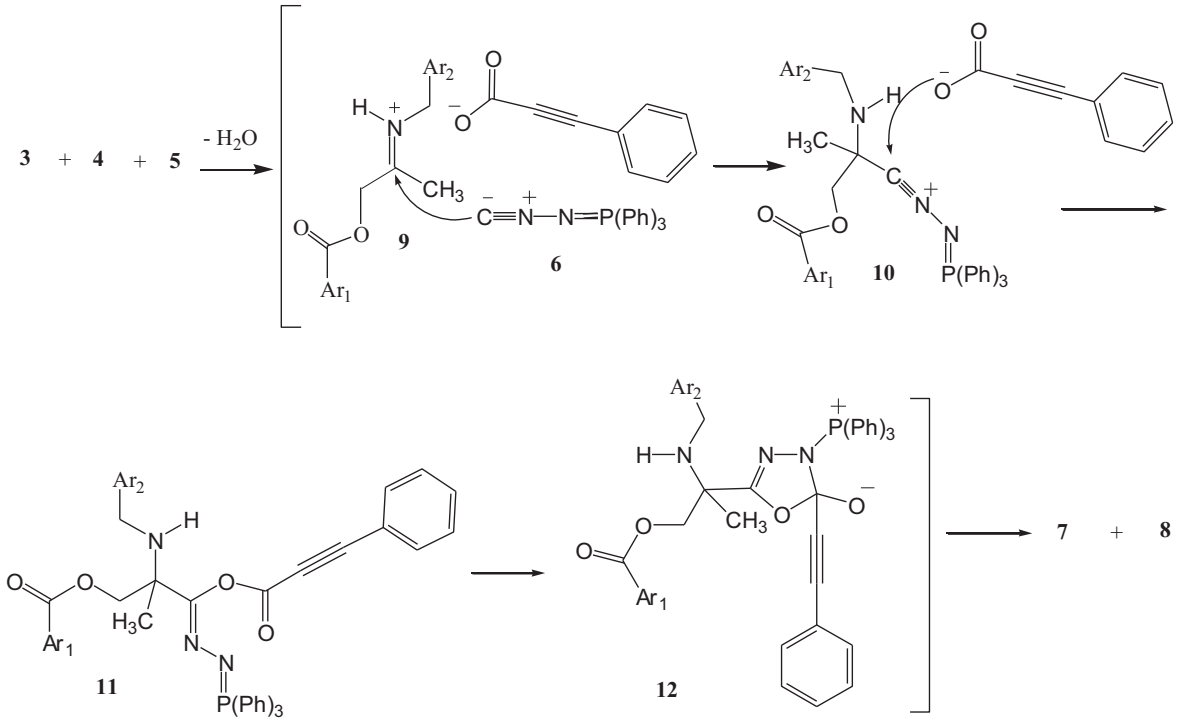
Table. Synthesis of disubstituted 1,3,4-oxadiazole derivatives 7 (see Scheme 1 and Figure).

Entry	Ketone **3**	Amine **5**	Acid **4**	Product
1	2-oxopropyl benzoate	benzylamine	3-phenyl-2-propynoic acid	**7a**
2	2-oxopropyl benzoate	4-methoxybenzylamine	3-phenyl-2-propynoic acid	**7b**
2	2-oxopropyl benzoate	4-methylbenzylamine	3-phenyl-2-propynoic acid	**7c**
4	2-oxopropyl 4-bromobenzoate	4-methylbenzylamine	3-phenyl-2-propynoic acid	**7d**
5	2-oxopropyl 4-bromobenzoate	2-chlorobenzylamine	3-phenyl-2-propynoic acid	**7e**
6	2-oxopropyl 4-bromobenzoate	2-furylmethanamine	3-phenyl-2-propynoic acid	**7f**
7	2-oxopropyl 4-bromobenzoate	2-methoxybenzylamine	3-phenyl-2-propynoic acid	**7g**
8	2-oxopropyl benzoate	2-methoxybenzylamine	3-phenyl-2-propynoic acid	**7h**
9	2-oxopropyl benzoate	2-furylmethanamine	3-phenyl-2-propynoic acid	**7i**
10	2-oxopropyl 4-bromobenzoate	4-methoxybenzylamine	3-phenyl-2-propynoic acid	**7j**
11	2-oxopropyl benzoate	1-naphthylmethanamine	3-phenyl-2-propynoic acid	**7k**

The structures of the products **7a-k** were deduced from their IR, ^{1}HNMR, and ^{13}CNMR spectra. For example the IR spectrum of **7a** showed strong absorptions at 3350 (NH), 2920 (CH), 2230 (C≡C), 1723 (C=O), 1453 (C=C, aromatic) and 708 (aromatic) cm^1 The ^{1}HNMR spectrum of **7a** consisted of a singlet for the CH_3 (δ = 1.79 ppm), a singlet for the NH of amine (δ = 2.24 ppm), a AB-quartet for CH_2 of the benzyl group (δ = 3.77 and 3.83 ppm, J = 12.50 Hz), a AB-quartet for CH_2 aliphatic (δ = 4.58 and 4.68 ppm, J = 11.0 Hz), and a multiplet for H-Ar (7.27-7.99 ppm). The ^{1}H decoupled ^{13}CNMR spectrum of **7a** showed 21 distinct resonances [δ= 20.9 (CH_3); 477 (CH_2, benzyl group); 56.9 (C, aliphatic); 69.0 (CH_2, aliphatic); 72.8 and 97.2 (2 C, acetylene); 119.6, 129.4, and 139.5 (3 C, arom.); 127.2, 128.1, 128.4, 128.5, 128.7, 129.7, 130.1, 132.5, and 133.3 (15 CH, arom.); 151.6 and 165.8 (2 C, oxadiazole); 168.6 (C of benzoate group)] that are in agreement with the formula and structure of **7a**. Partial assignment of these resonances is given in the spectral analysis section (see Experimental section). The ^{1}H and ^{13}CNMR spectra of compounds **7b**–**k** were similar to those of **7a**, except for the aromatic or heteroaromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

In summary, we have found a new method for the preparation of sterically congested 2,5-disubstituted 1,3,4-oxadiazole derivatives **7** from 3-phenyl-2-propynoic acid **4**, 2-oxopropyl benzoate (or 4-bromobenzoate) **3**, primary amine **5**, and *N*-isocyaniminotriphenylphosphorane **6** in excellent yields under neutral conditions. We

think that the reported method offers a mild and simple route for the preparation of these derivatives. Its ease of work-up and reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.



Scheme 2. Proposed mechanism for the formation of disubstituted 1,3,4-oxadiazole derivatives **7a-k**.

Conclusions

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.

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