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Preparation of sterically congested 1,3,4-oxadiazole derivatives from *N*-isocyaniminotriphenylphosphorane, aromatic acids, cyclopentanone and primary amines

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Abstract

Reactions of *N*-isocyaniminotriphenylphosphorane with cyclopentanone have been studied in the presence of aromatic carboxylic acids and primary amines. The reactions were proceeded smoothly at room temperature under neutral conditions in order to afford sterically congested 1,3,4-oxadiazole derivatives by an intramolecular Aza-Wittig cyclization in CH_2Cl_2 in excellent yields. The structures of the products were deduced from their IR, Mass, ^{1}H NMR, and ^{13}C NMR spectra. The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed. The method offers a mild, simple, and efficient route for the preparation of fully substituted 1,3,4-oxadiazoles from cyclopentanone, primary amines, *N*-isocyaniminotriphenylphosphorane and aromatic carboxylic acids. Easy work-up, high yields and fairly mild reaction conditions make it a useful procedure in comparison to the modern synthetic methodologies.

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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 selected products that retain the majority of the atoms of the starting material. The development of novel MCRs has received growing interest from industrial chemistry, research groups, and represents a challenge for organic chemists [1,2]. The efficient synthesis, toward simple and high yield, ideally one hundred percent, 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 significant role. Complex molecule total synthesis is often driven by step count while it experiences 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 three 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 has a wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, and antihypertensive [5-9]. Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. Most of 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]. In recent years, several synthetic methods have been reported for the preparation of *N*-isocyaniminotriphenylphosphorane ($CNNPPh_3$) **[**12,13]. It has been used in the synthesis of metal complexes [12,13]. However, application of **(4)** in the synthesis of organic compounds is fairly rare [14-23]. In recent years, we have established a one-pot method for the synthesis of oxadiazoles [14-22]. As part of our ongoing program to develop efficient methods for the preparation of heterocyclic compounds [24-35], we wish to report the synthesis of a disubstituted 1,3,4-oxadiazole derivatives **(5)** by a four-component condensation of *N*-isocyaniminotriphenylphosphorane **(4)** with cyclopentanone in the presence of aromatic carboxylic acids and primary amines *via* an Aza-Wittig cyclization in CH_2Cl_2 at ambient temperature in excellent yields (Scheme 1).

Experimental

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The progress of the reactions was monitored by TLC. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured ($CDCl_3$) 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-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Flash chromatography columns were prepared with Merck silica gel F_{254} powder.

General procedure for the preparation of Compounds 5a-l

To a magnetically stirred solution of benzyl amine derivatives **(1)** (1.0 mmol), cyclopentanone **(2)** (1.0 mmol) and *N*-isocyaniminotriphenylphosphorane **(4)** (1.0 mmol) in CH_2Cl_2 (5 mL) a solution of carboxylic acid **(3)** (1.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min at room temperature. The mixture was stirred for 3 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (petroleum ether-EtOAc (10:2)). The solvent was removed under reduced pressure and the pure products **(5a-l)** were obtained. The characterization data of the compounds are given below:

_N_-benzyl-_N_-{1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5a

Yellow oil, yield 300 mg (85%); R_f = 0.25 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3416 (NH), 2966 (C-H), 1457 (C=C, aromatic), 828 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.81-2.09 and 2.30-2.42 (m, 9H, CH_2 of cyclopentane and NH), 3.67 (s, 2H, CH_2 of benzyl group), 7.21-7.29 (m, 5H, H-Ar), 7.49 (d, 2H, J = 8.5 Hz, H-Ar), 7.98 (d, 2H, J = 8.5 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 23.9 and 37.6 ($4CH_2$, cyclopentane), 49.0 (CH_2 of benzyl group), 64.4 (C, cyclopentane), 122.5, 137.8 and 140.1 (3C, Ar), 127.0, 128.1, 128.1, 128.4 and 129.4 (9CH, Ar), 164.2 and 170.8 (2C=N). Analysis of $C_{20}H_{20}ClN_3O$ (353.8): calcd. C, 67.89; H, 5.70; N, 11.88. Found: C, 67.83; H, 5.74; N, 11.85. MS, *m/z* (%): 354 (M^+, 5), 324 (25), 313 (15), 262 (31), 248 (26), 220 (4), 139 (14), 111 (81), 91 (100), 65 (11), 41 (5).

_N_-benzyl-_N_-[1-(5-phenyl-1,3,4-oxadiazol-2-yl) cyclopentyl]amine 5b

Yellow oil, yield 249 mg (78%); R_f = 0.36 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3414 (NH), 2967 (C-H), 1517 (C=C, aromatic), 830 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.74-2.09 and 2.32-2.44 (m, 9H, CH_2 of cyclopentane and NH), 3.68 (s, 2H, CH_2 of benzyl group), 7.28-8.06 (m, 10H, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 23.9 and 37.6 ($4CH_2$, cyclopentane), 49.0 (CH_2 of benzyl group), 64.4 (C, cyclopentane), 124.0 and 140.2 (2C, Ar), 126.9, 127.0, 128.1, 128.4, 129.0 and 131.6 (10 CH, Ar), 164.9 and 170.6 (2C=N). Analysis of $C_{20}H_{21}N_3O$ (319.4): calcd. C, 75.21; H, 6.63; N, 13.16. Found: C, 75.28; H, 6.66; N, 13.12. MS, *m/z* (%): 319 (M^+, 4), 316 (7), 307 (46), 297 (18), 290 (43), 283 (98), 281 (77), 241 (19), 214 (89), 186 (19), 109 (70), 91 (100), 65 (13), 41 (5).

_N_-benzyl-_N_-{1-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5c

Yellow oil, yield 330 mg (83%); R_f = 0.28 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3415 (NH), 2955 (C-H), 1514 (C=C, aromatic), 825 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.81-2.09 and 2.30-2.41 (m, 9H, CH_2 of cyclopentane and NH), 3.67 (s, 2H, CH_2 of benzyl group), 7.21-7.28 (m, 5H, H-Ar), 7.65 (d, 2H, J = 8.25 Hz, H-Ar), 7.90 (d, 2H, J = 8.25 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 23.9 and 37.6 ($4CH_2$, cyclopentane), 49.0 (CH_2 of benzyl group), 64.4 (C, cyclopentane), 123.0, 126.3 and 140.1 (3C, Ar), 127.0, 128.1, 128.3, 128.4 and 132.3 (9CH, Ar), 164.2 and 170.8 (2C=N). Analysis of $C_{20}H_{20}BrN_3O$ (398.3): calcd. Anal. calc. for C, 60.31; H, 5.06; N, 10.55. Found: C, 60.34; H, 5.01; N, 10.61.

MS, *m/z* (%): 398 (M^+, 9), 317 (4), 308 (5), 292 (36), 214 (6), 186 (14), 174 (85), 106 (98), 91 (100), 82 (20), 65 (63), 54 (33), 41 (26).

_N_-{1-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}-_N_-(4-methylbenzyl)amine 5d

Yellow oil, yield 325 mg (79%); R_f = 0.51 (petroleum ether: AcOEt, 10:2); IR (neat): ν_{max} = 3414 (NH), 2962 (C-H), 1513 (C=C, aromatic), 830 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.82-2.08 and 2.25-2.32 (m, 9H, CH_2 of cyclopentane and NH), 2.25 (s, 3H, CH_3), 3.62 (s, 2H, CH_2 of benzyl group), 7.06 (d, 2H, *J* = 7.62 Hz, H-Ar), 7.15 (d, 2H, *J* = 7.62 Hz, H-Ar), 7.64 (d, 2H, *J* = 8.25 Hz, H-Ar), 7.89 (d, 2H, *J* = 8.25 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.0 (CH_3), 23.9 and 37.5 ($4CH_2$, cyclopentane), 48.7 (CH_2 of benzyl group), 64.3 (C, cyclopentane), 123.0, 126.2, 136.6 and 137.0 (4C, Ar), 128.0, 128.3, 129.0 and 132.3 (8CH, Ar), 164.3 and 170.9 (2C=N). Analysis of $C_{21}H_{22}BrN_3O$ (412.3): calcd. C, 61.17; H, 5.38; N, 10.19. Found: C, 61.14; H, 5.41; N, 10.15.

_N_-{1-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}-_N_-(4-methoxybenzyl)amine 5e

Yellow oil, yield 351 mg (82%); R_f = 0.34 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3417 (NH), 2928 (C-H), 1511 (C=C, aromatic), 830 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.82-2.05 and 2.29-2.35 (m, 9H, CH_2 of cyclopentane and NH), 3.60 (s, 2H, CH_2 of benzyl group), 3.73 (s, 3H, OCH_3), 6.78 (d, 2H, *J* = 6.25 Hz, H-Ar), 7.17 (d, 2H, *J* = 6.25 Hz, H-Ar), 7.64 (d, 2H, *J* = 6.25 Hz, H-Ar), 7.89 (d, 2H, *J* = 6.25 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 23.9 and 37.6 ($4CH_2$, cyclopentane), 48.4 (CH_2 of benzyl group), 55.2 (OCH_3), 64.3 (C, cyclopentane), 123.0, 126.2, 132.2 and 158.6 (4C, arom), 113.8, 128.2, 129.2 and 132.3 (8CH, arom), 164.2 and 170.9 (2C=N). Analysis of $C_{21}H_{22}BrN_3O_2$ (428.3): calcd. C, 58.89; H, 5.18; N, 9.81. Found: C, 58.85; H, 5.21; N, 9.76.

_N_-{1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}-_N_-(4-methoxybenzyl)amine 5f

Yellow oil, yield 321 mg (84%); R_f = 0.38 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3418 (NH), 2957 (C-H), 1512 (C=C, aromatic), 835 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.80-2.07 and 2.29-2.37 (m, 9H, CH_2 of cyclopentane and NH), 3.60 (s, 2H, CH_2 of benzyl group), 3.73 (s, 3H, OCH_3), 6.79 (d, 2H, *J* = 8.5 Hz, H-Ar), 7.18 (d, 2H, *J* = 8.5 Hz, H-Ar), 7.49 (d, 2H, *J* = 8.5 Hz, H-Ar), 7.97 (d, 2H, *J* = 8.5 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm):

23.9 and 37.6 ($4CH_2$, cyclopentane), 48.4 (CH_2 of benzyl group), 55.2 (OCH_3), 64.3 (C, cyclopentane), 122.5, 132.2, 137.8 and 158.6 (4C, Ar), 113.8, 128.1, 129.2 and 129.4 (8CH, Ar), 164.99 and 170.9 (2C=N). Analysis of $C_{21}H_{22}ClN_3O_2$ (383.1): calcd. Anal. calc. for C, 65.71; H, 5.78; N, 10.95. Found: C, 65.76; H, 5.82; N, 10.91.

***N*-(4-methoxybenzyl)-*N*-{1-[5-(4-methyphenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5g**

Yellow oil, yield 312 mg (86%); R_f = 0.38 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3418 (NH), 2955 (C-H), 1512 (C=C, aromatic), 824 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.80-2.07 and 2.30-2.37 (m, 9H, CH_2 of cyclopentane and NH), 2.43 (s, 3H, CH_3), 3.60 (s, 2H, CH_2 of benzyl group), 3.79 (OCH_3), 6.80 (d, 2H, J = 8.25 Hz, H-Ar), 7.19 (d, 2H, J = 8.25 Hz, H-Ar), 7.31 (d, 2H, J = 7.87 Hz, H-Ar), 7.92 (d, 2H, J = 7.87 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.6 (CH_3), 23.9 and 37.5 ($4CH_2$, cyclopentane), 48.4 (CH_2 of benzyl group), 55.2 (OCH_3), 64.3 (C, cyclopentane), 121.3, 132.3, 142.0 and 158.6 (4C, Ar), 113.8, 126.8, 129.3 and 129.7 (8CH, Ar), 164.4 and 170.4 (2C=N). Analysis of $C_{22}H_{25}N_3O_2$ (363.5): calcd. for C, 72.70; H, 6.93; N, 11.56. Found: C, 72.76; H, 6.97; N, 11.53.

***N*-(4-methylbenzyl)-*N*-{1-[5-(4-methyphenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5h**

Yellow oil, yield 278 mg (80%); R_f = 0.58 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3415 (NH), 2953 (C-H), 1513 (C=C, aromatic), 823 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.81-2.05 and 2.26-2.38 (m, 9H, CH_2 of cyclopentane and NH), 2.26 and 2.43 (2s, 6H, $2CH_3$), 3.62 (s, 2H, CH_2 of benzyl group), 7.07 (d, 2H, J = 7.50 Hz, H-Ar), 7.16 (d, 2H, J = 7.50 Hz, H-Ar), 7.31 (d, 2H, J = 8 Hz, H-Ar), 7.92 (d, 2H, J = 8 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.0 and 21.6 ($2CH_3$), 23.9 and 37.5 ($4CH_2$, cyclopentane), 48.8 (CH_2 of benzyl group), 64.3 (C, cyclopentane), 121.3, 137.2, 142.0 and 159.4 (4C, Ar), 126.8, 128.0, 129.0 and 129.7 (8CH, Ar), 163.9 and 170.4 (2C=N). Analysis of $C_{22}H_{25}N_3O$ (347.5): calcd. C, 76.05; H, 7.25; N, 12.09. Found: C, 76.01; H, 7.31; N, 12.12.

***N*-(2-methoxybenzyl)-*N*-{1-[5-(4-methyphenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5i**

Yellow oil, yield 269 mg (74%); R_f = 0.29 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3415 (NH), 2955 (C-H), 1498 (C=C, aromatic), 825 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.79-2.09 and 2.35-2.43 (m, 9H, CH_2 of cyclopentane and NH), 2.43 (s,

3H, CH_3), 3.66 (s, 2H, CH_2 of benzyl group), 3.71 (OCH_3), 6.72-7.91 (m, 8H, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.6 (CH_3), 23.9 and 37.3 ($4CH_2$, cyclopentane), 44.5 (CH_2 of benzyl group), 55.2 (OCH_3), 64.2 (C, cyclopentane), 121.2, 128.0, 142.1 and 158.6 (4C, Ar), 110.1, 120.5, 126.8, 128.26, 129.6 and 129.8 (8CH, Ar), 164.2 and 170.4 (2C=N). Analysis of $C_{22}H_{25}N_3O_2$ (363.5): calcd. C, 72.70; H, 6.93; N, 11.56. Found: C, 72.74; H, 6.90; N, 11.50.

***N*-benzyl-*N*-{1-[5-(2,4-dimethylphenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5j**

Yellow oil, yield 245 mg (71%); R_f = 0.29 (petroleum ether: EtOAc 10:2); IR (neat): ν_{max} = 3415 (NH), 2956 (C-H), 1452 (C=C, aromatic), 823 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.81-2.06 and 2.31-2.39 (m, 9H, CH_2 of cyclopentane and NH), 2.39 and 2.67 (2s, 6H, $2CH_3$), 3.68 (s, 2H, CH_2 of benzyl group), 7.11-7.29 (m, 7H, H-Ar), 7.80 (d, 1H, J = 7.75 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.4 and 22.0 ($2CH_3$), 23.9 and 37.6 ($4CH_2$, cyclopentane), 49.0 (CH_2 of benzyl group), 64.3 (C, cyclopentane), 120.3, 138.2, 140.2 and 141.5 (4C, Ar), 126.9, 127.0, 128.2, 128.4, 128.9 and 132.5 (8CH, Ar), 164.9 and 170.3 (2C=N). Analysis of $C_{22}H_{25}N_3O$ (347.5): calcd. Anal. calc. for C, 76.05; H, 7.25; N, 12.09. Found: C, 76.01; H, 7.30; N, 12.05.

***N*-benzyl-*N*-{1-[5-(4-ethylphenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5k**

Yellow oil, yield 281 mg (81%); R_f = 0.29 (petroleum ether:EtOAc, 10:2); IR (neat): ν_{max} = 3415 (NH), 2955 (C-H), 1500 (C=C, aromatic), 788 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.28 (t, 3H, J = 7.5 Hz, CH_3 of Ethyl), 1.81-2.08 and 2.31-2.41 (m, 9H, CH_2 of cyclopentane and NH), 2.73 (q, 2H, J = 7.5 Hz, CH_2 of Ethyl), 3.66 (s, 2H, CH_2 of benzyl group), 7.20-7.30 (m, 5H, H-Ar), 7.34 (d, 2H, J = 8.12 Hz, H-Ar), 7.96 (d, 2H, J = 8.12 Hz, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 15.3 (CH_3), 28.9 (CH_2 of Ethyl), 23.9 and 37.5 ($4CH_2$, cyclopentane), 49.0 (CH_2 of benzyl group), 64.4 (C, cyclopentane), 121.5, 140.2 and 148.4 (3C, Ar), 126.9, 127.0, 128.1, 128.4 and 128.5 (9CH, Ar), 165.1 and 170.3 (2C=N). Analysis of $C_{22}H_{25}N_3O$ (347.5): calcd. Anal. calc. for C, 76.05; H, 7.25; N, 12.09. Found: C, 76.08; H, 7.22; N, 12.12.

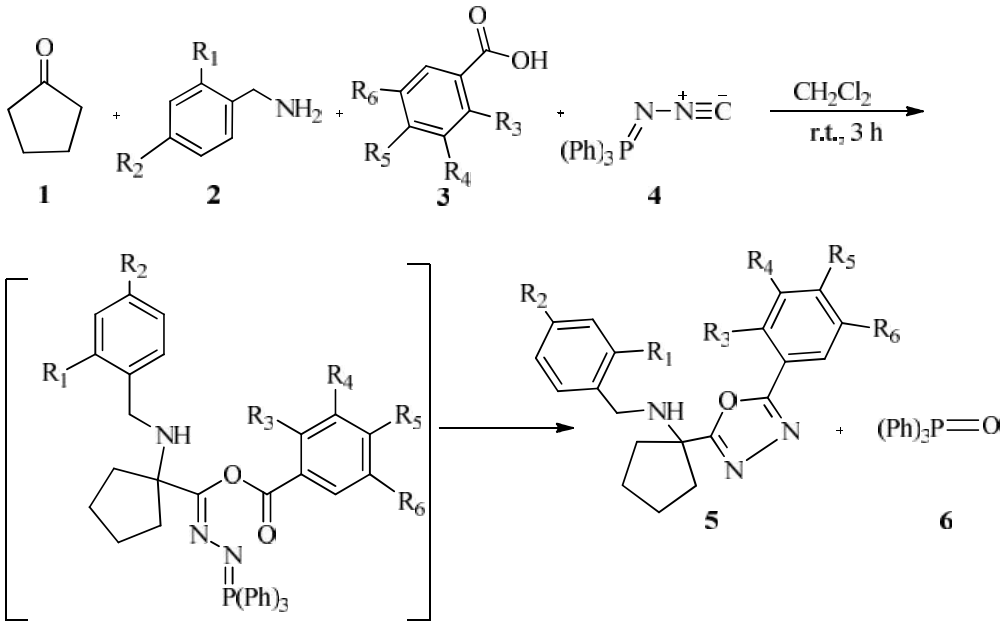
***N*-benzyl-*N*-{1-[5-(3,5-dimethylphenyl)-1,3,4-oxadiazol-2-yl]cyclopentyl}amine 5l**

Yellow oil, yield 264 mg (76%); R_f = 0.32 (petroleum ether: EtOAc, 10:2); IR (neat): ν_{max} = 3415 (NH), 2955 (C-H), 1452 (C=C, aromatic), 857 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.81-2.09 and 2.31-2.40 (m, 9H, CH_2 of cyclopentane and NH), 2.40 (s, 6H, $2CH_3$), 3.65 (s, 2H, CH_2 of benzyl

group), 7.17-7.30 (m, 6H, H-Ar), 7.66 (s, 2H, H-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 21.2 ($2CH_3$), 23.9 and 37.5 ($4CH_2$, cyclopentane), 49.0 (CH_2 of benzyl group), 64.39 (C, cyclopentane), 123.6, 127.0 and 140.1 (3C, Ar), 124.6, 128.1, 128.4, 133.3 and 138.8 (8CH, Ar), 164.4 and 170.4 (2C=N). Analysis of $C_{22}H_{25}N_3O$ (347.5): calcd. C, 76.05; H, 7.25; N, 12.09. Found: C, 76.09; H, 7.20; N, 12.12.

Results and Discussion

The imine intermediate that is generated from the reaction of primary amine (**2**) with cyclopentanone **(1)** is trapped by the *N*-isocyaniminotriphenylphosphorane **(4)** in the presence of an aromatic carboxylic acid **(3)** to afford the disubstituted 1,3,4-oxadiazoles **(5).** Triphenylphosphine oxide **(6)** is the by-product of the reaction (Scheme 1). The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed.



5a: R_1=H, R_2=H, R_3=H, R_4=H, R_5=Cl, R_6=H **5b:** R_1=H, R_2=H, R_3=H, R_4=H, R_5=H, R_6=H; **5c:** R_1=H, R_2=H, R_3=H, R_4=H, R_5=Br, R_6=H; **5d:** R_1=H, R_2=CH_3, R_3=H, R_4=H, R_5=Br, R_6=H; **5e:** R_1=H, R_2=OCH_3, R_3=H, R_4=H, R_5=Br, R_6=H; **5f:** R_1=H, R_2=OCH_3, R_3=H, R_4=H, R_5=Cl, R_6=H; **5g:** R_1=H, R_2=OCH_3, R_3=H, R_4=H, R_5=CH_3, R_6=H; **5h:** R_1=H, R_2=CH_3, R_3=H, R_4=H, R_5=CH_3, R_6=H; **5i:** R^1=OCH_3, R_2=H, R_3=H, R_4=H, R_5=CH_3, R_6=H; **5j:** R_1=H, R_2=H, R_3=CH_3, R_4=H, R_5=CH_3, R_6=H; **5k:** R_1=H, R_2=H, R_3=H, R_4=H, R_5=Et, R_6=H; **5l**: R_1=H, R_2=H, R_3=H, R_4=CH_3, R_5=H, R_6=CH_3

Scheme 1: Synthesis of disubstituted 1,3,4-oxadiazole derivatives **5a-l**

The structures of the products were deduced from their IR, Mass, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. For example the IR spectrum of **5a** showed strong absorptions at 3416 (NH), 2966 (CH), 1457 (C=C, aromatic) and 828 cm^{-1}. The ^{1}H NMR spectrum of **5a** consisted of two multiple at δ= 1.81-2.09 and 2.30-2.42 ppm for CH_2 of

cyclopentane and NH of amine, a singlet at ¢ = 3.67 ppm for CH_2 of benzyl group, two doublet at ¢ = 7.49 and 7.98 ppm with *J*= 8.5 Hz and a multiplet at ¢ = 7.21-7.29 ppm for aromatic hydrogens. The ^{13}C NMR spectrum of **5a** is in agreement with the proposed structure. In view of the success of the above-mentioned reaction, we explored the scope of this promising reaction with a variety of carboxylic acids and amines **(Table 1)**. Owing to the great diversity of substitution patterns, this reaction may be used in the production of a great library of disubstituted 1,3,4-oxadiazoles.

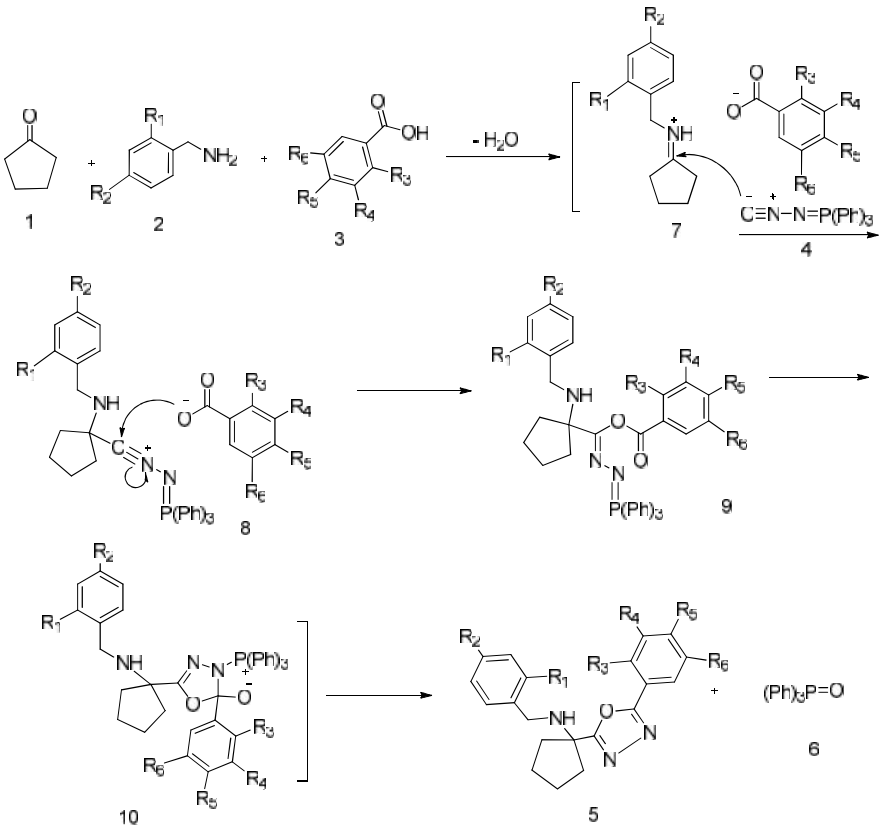
Table 1: Synthesis of disubstituted 1,3,4-oxadiazole derivatives **5a-l** from cyclopentanone, amines **(2)** and carboxylic acids **3** in the presence of *N*-isocyaniminotriphenylphosphorane **(4)**

Products	2	3	Yield[a](%)
5a	C_6H_5-CH_2NH_2	4-ClC_6H_4-CO_2H	85
5b	C_6H_5-CH_2NH_2	C_6H_5-CO_2H	78
5c	C_6H_5-CH_2NH_2	4-BrC_6H_4-CO_2H	83
5d	4-MeC_6H_4-CH_2NH_2	4-BrC_6H_4-CO_2H	79
5e	4-MeOC_6H_4-CH_2NH_2	4-BrC_6H_4-CO_2H	82
5f	4-MeOC_6H_4-CH_2NH_2	4-ClC_6H_4-CO_2H	84
5g	4-MeOC_6H_4-CH_2NH_2	4-MeC_6H_4-CO_2H	86
5h	4-MeC_6H_4-CH_2NH_2	4-MeC_6H_4-CO_2H	80
5i	2-MeOC_6H_4-CH_2NH_2	4-MeC_6H_4-CO_2H	74
5j	C_6H_5-CH_2NH_2	2,4-$Me_2C_6H_3$-CO_2H	71
5k	C_6H_5-CH_2NH_2	4-EtC_6H_4-CO_2H	81
5l	C_6H_5-CH_2NH_2	3,5-$Me_2C_6H_3$-CO_2H	76

[a]Yield of isolated products

A mechanistic rationalization for this reaction is provided in Scheme 2. It is conceivable that, the initial event is the condensation of the cyclopentanone **(1)**, benzyl amine derivatives **(2)** and carboxylic acids **(3)** produces an iminium carboxylate salt intermediate **(7)**. The Nucleophilic addition of the *N*-isocyaniminotriphenylphosphorane **(4)** to **(7)**, lead to nitrilium intermediate **(8)**. This

intermediate may be attacked by the conjugate base of the carboxylic acid to form the adduct **(9)** which undergoes an intramolecular Aza-Wittig reaction to afford the 2,5-disubstituted 1,3,4-oxadiazole **(5)** by the removal of triphenylphosphine oxide **(6)** from **10**.



Scheme 2. A possible mechanism for the formation of products **5a-l**

Conclusion

The reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazole derivatives **(5)** from the multicomponent condensation of cyclopentanone **(1)**, primary amines **(2),** *N*-isocyaniminotriphenylphosphorane **(4)**, and aromatic carboxylic acids **(3)**. The ease of work-up, high yields, and fairly mild reaction conditions make it a useful procedure in relation to the modern synthetic methodologies.

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