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Synthesis and Characterization of Some 1,3,4-oxadiazole derivatives

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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 dichloro methanein excellent yields. The structures of the products were deduced from their IR, Mass, ^{1}H NMR, and ^{13}C NMR spectra. The method offers a mild, simple, and efficient route for the preparation of fully substituted1,3,4-oxadiazoles from cyclopentanone, primaryamines, *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.

Keywords: *N*-isocyaniminotriphenylphosphorane, cyclopentanone, aromatic carboxylic acids, primary amines, 1,3,4-oxadiazole.

Introduction

The synthesis of high nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications such as propellants, explosives, pyrotechnics and especially chemotherapy. Among these heterocycles the 1,3,4-oxadiazole motif is of particular value in materials science, agrochemistry and in pharmaceutical chemistry. A number of synthetic routes have been developed for 1,3,4-oxadiazole. Majority of these are based upon cyclodehydration of diacylhydrazines. Similarly 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biologicalimportancethus, a large number of 1,2,4-triazole containing ring system have been used in a wide variety of applications as inhibitors of corrosion, polymers, drugs candidates and as synthetic dyes.

In addition, phthalimides are bicyclic nitrogen heterocycles constitute an important class of compounds with a variety of applications and a wide range of properties. Generally they are used as starting materials and intermediates for synthesis of many types of alkaloids and pharmacophores, in polymers, synthesis of pesticides and lately are being under intense biomedical research due to their important biological effects.

In recent years, several synthetic methods have been reported for the preparation of *N* isocyaniminotriphenylphosphorane ($CNNPPh_3$). In recent years, we have established a onepot method for the synthesis of oxadiazoles. As part of our ongoing program to develop efficient methods for the preparation of heterocyclic compounds, we wish to report the synthesis of a disubstituted 1,3,4-oxadiazole derivatives by a four-component condensation of *N*-isocyaniminotriphenyl phosphoranewith cyclopentanone in the presence of aromatic carboxylic acids and primary amines *via* an Aza-Wittig cyclization in dichloromethaneat ambient temperature in excellent yields (Scheme 1).

Experimental

Starting materials and solvents were obtained from Merck 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 gelF_{254} powder.

General procedure for the preparation of Compounds 1a - h

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 **(1a-h)** were obtained. The characterization data of the compounds are given below

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

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}. ^{1}H 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(1b)

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)-1,3,4oxadiazol-2-yl]cyclopentyl} amine (1c)

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-oxadiazol2-yl]cyclopentyl}-*N*-(4methylbenzyl) amine (1d)

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-oxadiazol2-yl]cyclopentyl}-*N*-(4methoxybenzyl) amine (1e)

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} . ^{1}H 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, HAr). ^{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.

N-{1-[5-(4-chlorophenyl)-1,3,4-oxadiazol2-yl]cyclopentyl}-*N*-(4methoxybenzyl) amine (1f)

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}. ^{1}H 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, HAr). ^{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-(4methyphenyl)-1,3,4-oxadiazol-2yl]cyclopentyl} amine (1g)

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} . ^{1}H 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, HAr), 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.

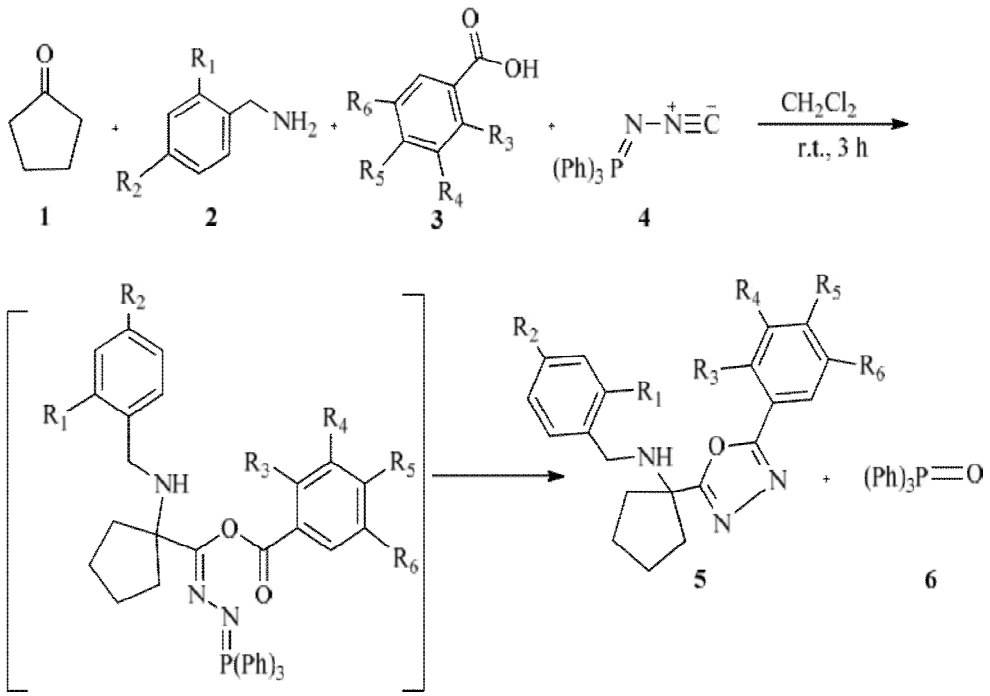
N-(4-methylbenzyl)-*N*-{1-[5-(4methyphenyl)-1,3,4-oxadiazol-2yl]cyclopentyl} amine (1h)

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 . H 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, HAr), 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.

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 byproduct of the reaction (Scheme 1). The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed.

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 tspectrum of **1a** showed strong absorptions at3416 (NH), 2966 (CH), 1457 (C=C, aromatic) and 828 cm^{-1}. The ^{1}H NMR spectrum of **1a** 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 **1a** is in agreement with the proposed structure above-mentioned reaction, we explored the scope of this promising reaction with a varietyof 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.



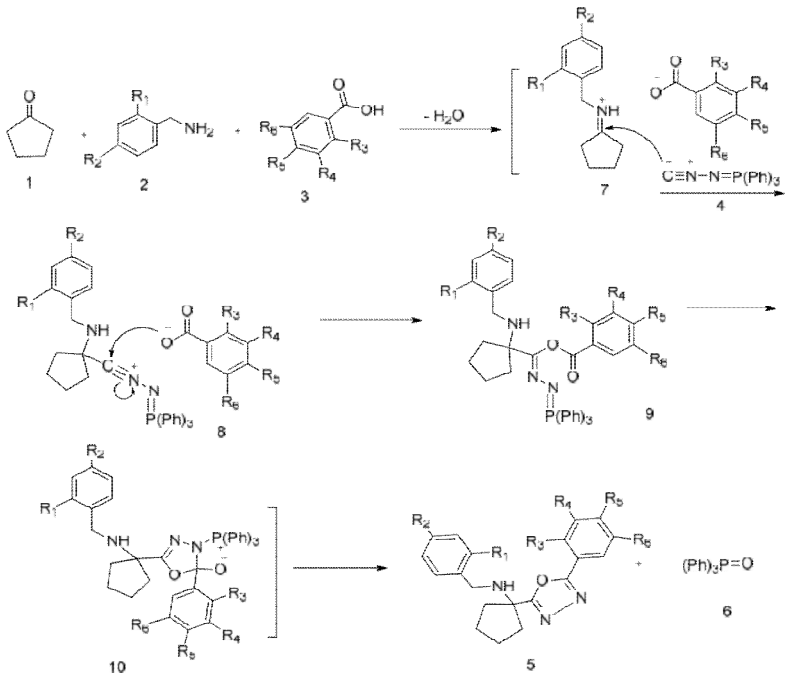
5a: R_1=H, R_2=H, R_3=H, R_4=H, R_5=Cl, R_6=H **5b:** R_1=H, R_2=H, R_3=H, R_4=H, R_5=H, R_6=H; **5c:** R_1=H, R_2=H, R_3=H, R_4=H, R_5=Br, R_6=H; **5d:** R_1=H, R_2=CH_3, R_3=H, R_4=H, R_5=Br, R_6=H; **5e:** R_1=H, R_2=OCH_3, R_3=H, R_4=H, R_5=Br, R_6=H; **5f:** R_1=H, R_2=OCH_3, R_3=H, R_4=H, R_5=Cl, 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.

Scheme 1.Synthesis of disubstituted 1,3,4-oxadiazole derivatives 1a-h

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

Products	2	3	Yield[a](%)
1a	C6H5-CH2NH2	4-ClC_6H_4-CO_2H	85
1b	C6H5-CH2NH2	C_6H_5-CO_2H	78
1c	C6H5-CH2NH2	4-BrC_6H_4-CO_2H	83
1d	4-MeC_6H_4-CH_2NH_2	4-BrC_6H_4-CO_2H	79
1e	4-$MeOC_6H_4$-CH_2NH_2	4-BrC_6H_4-CO_2H	82
1f	4-$MeOC_6H_4$-CH_2NH_2	4-ClC_6H_4-CO_2H	84
1g	4-$MeOC_6H_4$-CH_2NH_2	4-MeC_6H_4-CO_2H	86
1h	4-MeC_6H_4-CH_2NH_2	4-MeC_6H_4-CO_2H	80

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 theconjugate base of the carboxylic acid to form the adduct**(9)** which undergoes 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-h

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 syntheticmethodologies.

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