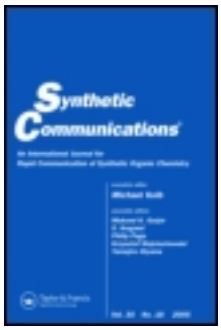

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# Four-Component Synthesis of Disubstituted 1,3,4-oxadiazoles From N-Isocyaniminotriphenylphosphorane, Phenylacetylenecarboxylic Acid, Chloroacetone Derivatives and Primary Amines

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# Four-component Synthesis of Disubstituted 1,3,4-Oxadiazoles from *N*-Isocyaniminotriphenylphosphorane, Phenylacetylenecarboxylic Acid, Chloroacetone Derivatives and Primary Amines

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## Abstract

The 1:1 imine intermediate generated by the addition of primary amine to chloroacetone derivatives is trapped by *N*-isocyaniminotriphenylphosphorane in the presence of phenylacetylenecarboxylic acid leading to the formation of the corresponding iminophosphorane intermediate. Disubstituted 1,3,4-oxadiazole derivatives are formed *via* intramolecular *aza*-Wittig reaction of the iminophosphorane intermediate. The reactions were completed in neutral conditions at room temperature. The disubstituted 1,3,4-oxadiazole derivatives, were prepared in excellent yields.

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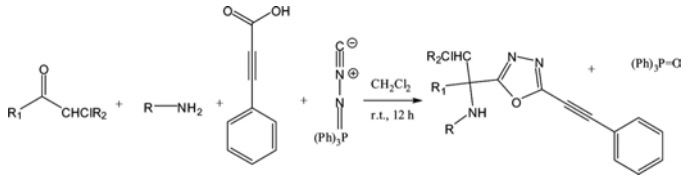

**KEYWORDS:** *N*-Isocyaniminotriphenylphosphorane, chloroacetone derivatives, Phenylacetylenecarboxylic Acid, 1,3,4-Oxadiazole, Aza-Wittig reaction, Primary Amine

## INTRODUCTION

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without any isolation of intermediates or changes of the conditions.[1–9] This principle, therefore, is highly efficient in terms of time as well as resources.[10] Among the multicomponent reactions known to date, the most valuable reactions are those based on isocyanides. Isocyanide-based multicomponent reactions (abbreviated to IMCRs by Ugi and Dömling) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.[11-13]

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. Several interesting hetero-cyclization reactions involving iminophosphoranes have been reviewed.[14] These

compounds can easily be converted through *aza*-Wittig reaction with isocyanates, carbon dioxide, or carbon disulfide into functionalized hetero-cumulenes which exhibit a rich chemistry of unusual synthetic promise.[14-16] 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.[14-17] In the last years, several preparative procedures have been reported for the preparations and synthetic applications of iminophosphoranes.[17] *N*-isocyaniminotriphenylphosphorane **4** is expected to have synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality.[17] In recent years, we have established a one-pot method for the preparation of organophosphorus compounds.[18-24]



1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides.[25-27] 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.[25-27] Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multi-step in nature.[28-30] 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.[31] As part of our ongoing program to develop efficient and robust methods for

the synthesis of heterocyclic compounds,[32-42] we wish to report the preparation of a new class of 1,3,4-oxadiazole derivatives **5a-t** by a novel four-component condensation reaction of chloroacetone derivatives **1**, primary amine **2**, *N*-isocyaniminotriphenylphosphorane **4** and phenylacetylenecarboxylic acid **3** in excellent yields under neutral conditions (Scheme 1).

## RESULTS AND DISCUSSION

The 1:1 imine intermediate generated by the condensation reaction of primary amine **2** with chloroacetone derivatives **1** is trapped by the *N*-isocyaniminotriphenylphosphorane **4** in the presence of phenylacetylenecarboxylic acid **3** leading to the formation of 1,3,4-oxadiazole derivatives **5** and triphenylphosphine oxide **6** (Scheme **1** and Table **1**). The reaction proceeds with the high efficiency towards the desired output products under mild and neutral conditions and no side reactions were observed. The structures of the products were deduced from their $^{1}$H NMR, $^{13}$C NMR, IR and Mass spectra.

**4a**: $R_1$= $CH_3$, $R_2$= H, R= 4-methoxybenzyl; **4b**: $R_1$= $CH_2Cl$, $R_2$= H, R= 4-methoxybenzyl; **4c**: $R_1$= $CH_3$, $R_2$= H, R= allyl; **4d**: $R_1$= $CH_3$, $R_2$= H, R= 4-methylbenzyl; **4e**: $R_1$= $CH_3$, $R_2$= H, R= benzyl **4f**: $R_1$= $CH_2Cl$, $R_2$= H, R= benzyl; **4g**: $R_1$= $CH_3$, $R_2$= H, R= furfuryl; **4h**: $R_1$= $CH_2Cl$, $R_2$= H, R= 4-methylbenzyl; **4i**: $R_1$= $CH_3$, $R_2$= H, R= 4-fluorobenzyl; **4j**: $R_1$= $CH_2Cl$, $R_2$= H, R= naphthyl; **4k**: $R_1$= $CH_3$, $R_2$= Cl, R= 4-methoxybenzyl; **4l**: $R_1$= $CH_3$, $R_2$= H, R= 2-chlorobenzyl; **4m**: $R_1$= $CH_2Cl$, $R_2$= H, R= furfuryl, **4n**: $R_1$= $CH_3$, $R_2$= Cl, R= benzyl; **4o**: $R_1$= $CH_2Cl$, $R_2$= H, R= 2-chlorobenzyl; **4p**: $R_1$= $CH_3$, $R_2$= H, R= 3,4-dichorobenzyl; **4q**: $R_1$= $CH_3$, $R_2$= Cl, R= 4-methylbenzyl; **4r**: $R_1$= $CH_3$, $R_2$= H, R= naphthyl; **4s**: $R_1$= $CH_3$, $R_2$= Cl, R= allyl; **4t**: $R_1$= $CH_2Cl$, $R_2$= H, R= allyl.

A mechanistic pathway for the reaction is provided in Scheme 2. On the basis of the chemistry of isocyanides, it is reasonable to assume that the first step may involve the formation of imine **7** by the condensation reaction of primary amine **2** with chloroacetone derivative **1**, the next step may involve nucleophilic addition of the *N*-isocyaniminotriphenylphosphorane **4** to the imine intermediate **7**, which is facilitated by its protonation with the phenylacetylenecarboxylic acid **3**, leading to nitrilium intermediate **8**. This intermediate may be attacked by conjugate base of the carboxylic acid to form 1:1:1 adduct **9**. The intermediate **9** may undergo intramolecular *aza*-Wittig reaction[32–42] of iminophosphorane moiety with the ester carbonyl to afford the isolated sterically congested 1,3,4-oxadiazole derivatives **5** by removal of triphenylphosphine oxide **6** from intermediate **10**. It seems that the intramolecular *aza*-Wittig reaction of intermediate **9** occurs much faster than its acyl group migration such as in normal Ugi reaction.[12] We try to investigate the presented mechanism in the Scheme 2 by $^{13}$P NMR at room temperature, but the detection of the intermediates at room temperature was fairly impossible. It seems that the low life time of the intermediates at room temperature is the reason of this impossibility. We hope to invetigate the mechanism by using dynamic $^{13}$P NMR at low temperature in future studies.



## CONCLUSIONS

We think that the reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazol derivatives of type **5**. Ease of work-

up, high yields and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this synthetic process are under investigation.

## EXPERIMENTAL SECTION

### General Procedures

*N*-Isocyaniminotriphenylphosphorane **4** was prepared based on reported procedures.[17] Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions are TLC and NMR. TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. $^{1}H$ and $^{13}C$- NMR spectra ($CDCl_3$) were recorded on a BRUKER DRX-250AVANCE spectrometer at 250.0 and 62.9 MHz, respectively. IR spectra were measured on a Jasco 6300 FTIR spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Preparative layer chromatography (PLC) plates were prepared from Merck silica gel ($F_{254}$) powder.



### PREPARATION OF *N*-ISOCYANIMINOTRIPHENYLPOSPHORANE 4

$CH_2Cl_2$ (300 mL), $PPh_3$ (52.5 g, 0.2 mol), $NEt_3$ (23 mL) and formylhydrazine (5.1 g, 0.08 mol) were placed in a reaction flask. The slurry was then heated to 50–60 °C, and $CCl_4$ (16.1 mL) was added dropwise over a period of about 30 min. The mixture was kept at 50–60 °C for at least 5–6 h. After cooling to room temperature, 100 mL of a saturated aqueous $Na_2CO_3$ solution was added, the layers were separated, and the aqueous layer

was washed with two 25 mL portions of $CH_2Cl_2$. The combined organic phases were dried with $Na_2SO_4$ and filtered. After evaporation of the solvent, the residue was dried under high vacuum, pulverised, stirred in 100 mL of ethanol/water (1:1.5) and collected on a frit. Recrystallisation from hot ethanol yielded 7.0 g (30%) of an orange-brown crystalline material **4** (m.p. 159–160 °C).[17]

**GENERAL PROCEDURE FOR THE PREPARATION OF COMPOUNDS 5A-T**

To a magnetically stirred solution of primary amine derivatives (1 mmol), chloroacetone derivatives (1 mmol), and *N*-isocyaniminotriphenylphosphorane (1 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise a solution of phenylacetylenecarboxylic acid (1 mmol) in $CH_2Cl_2$ (5 mL) at room temperature over 15 min. The mixture was stirred for 12 h. The solvent was removed under reduced pressure, and the viscous residue was purified by preparative layer chromatography (PLC) plates (Merck silica gel ($F_{254}$) powder; petroleum ether-ethyl acetate (4:1)). The characterization data of the compounds are given below.

**N-{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(4-METHOXYLBENZYL)AMINE (5A).**

Yellow viscose oil; yield: 89%; $^1$H NMR ($CDCl_3$): $\delta$ = 1.73 (s, 3H, $CH_3$), 2.13 (s, 1H, NH), 3.60 and 3.67 ($AB_q$, $J$ =12.3 Hz , 2H, $CH_2$), 3.77 (s, 3H, $OCH_3$), 3.90 and 3.99 ($AB_q$, $J$ = 11.3 Hz, 2H, $CH_2$ of benzyl), 6.84 (d, $J$ = 8.5 Hz, 2H, $CH_{arom}$ ), 7.23 (d, $J$ = 8.5 Hz, 2H, $CH_{arom}$), 7.39-7.65 (m, 5H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 22.29 ($CH_3$), 47.16, 50.07 ($2CH_2$), 55.26 ($OCH_3$), 57.73 (C-NH), 113.92, 128.70, 129.44, 130.73,

132.36 (9CH), 73.41, 97.96, 119.67, 131.26, 154.94, (5C), 158.91, 168.36 (2C=N). IR (KBr): $v$ = 3431, 2949, 2847, 2231, 1611, 1509, 1441, 1247, 822, 756, 688 $cm^{-1}$. MS: *m/z* (%); 382 ($M^+$, 4), 345 (52), 211 (68), 136 (92), 121 (100), 91(32), 77 (60), 41(28). Anal.Calcd.for $C_{21}H_{20}ClN_3O_2$ (381.12): C, 66.05; H, 5.28; N, 11.00 %. Found: C, 66.11; H, 5.22; N, 11.06 %.

**N-{2–CHLORO–1–(CHLOROMETHYL)–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(4-METHOXYBENZYL)AMINE (5B).**

Yellow powder; yield: 92%; m.p. 82-84ºC; $^1$H NMR ($CDCl_3$): $\delta$ = 2.06 (s, 1H, NH), 3.57 (s, 2H, $CH_2$ of benzyl), 3.76 (s, 3H, $OCH_3$), 4.16 (s, 4H, $2CH_2$), 6.84 (d, $J$ = 7.5 Hz, 2H, $CH_{arom}$), 7.19 (d, $J$ = 7.5 Hz, 2H, $CH_{arom}$), 7.40-7.66 (m, 5H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 44.34 ($2CH_2$), 46.96 ($CH_2$ of benzyl), 55.26 ($OCH_3$), 61.51 (C-NH), 113.93, 128.73, 129.50, 130.87, 132.41 (9CH), 73.67, 97.24, 119.52, 130.35, 159.07 (5C), 164.92, 165.03 (2C=N). IR (KBr): $v$ = 3456, 2923, 2851, 2231, 1611, 1512, 1464, 1248, 823, 745 $cm^{-1}$. MS: *m/z* (%); 416 ($M^+$), 352 (20), 245 (20), 211 (56), 167 (28), 149 (52), 136 (64), 120 (84), 105 (100), 91 (21), 69(24), 41 (16). Anal.Calcd.for $C_{21}H_{19}Cl_2N_3O_2$ (416.30): C, 60.59; H, 4.60; N, 10.09%. Found: C, 60.64; H, 4.65; N, 10.14%.

**N-ALLYL-N-{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL} AMINE (5C).**

Yellow viscose oil; yield: 93%; $^1$H NMR ($CDCl_3$): $\delta$ = 1.69 (s, 3H, $CH_3$), 2.10 (s, 1H, NH), 3.17 (m, 2H, $CH_2$ of allyl), 3.87 and 3.91 ($AB_q$, $J$ = 11.3Hz, 2H, $CH_2$), 5.20 (m,

2H, $=CH_2$), 5.85 (m, 1H, =CH), 7.41-7.61 (m, 5H, $CH_{arom}$). $^{13}C$ NMR($CDCl_3$): $\delta$ = 22.19 ($CH_3$), 46.14, 50.02 ($2CH_2$), 57.92 (C-NH), 128.70, 132.00, 132.35, 135.59 (6CH), 116.80 ($=CH_2$), 73.54, 97.42, 119.72 (3C), 161.28, 168.46 (2C=N). IR (KBr): $v$ = 3436, 3924, 2852, 2231, 1644, 1538, 1443, 1022, 757, 688 $cm^{-1}$. MS: *m/z* (%); 302 ($M^+$, 15), 266 (11), 252 (46), 232 (23), 211 (100),129 (61), 96 (46), 70 (96), 56 (88), 42 (88). Anal.Calcd.for $C_{16}H_{16}ClN_3O$ (301.77): C, 63.68; H, 5.34; N, 13.92%. Found: C, 63.74; H, 5.40; N, 13.98%.



**N-{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(4-METHYLBENZYL)AMINE (5D).**

Yellow viscose oil; Yield: 89%; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.74 (s, 3H, $CH_3$), 2.07 (s, 1H, NH), 2.31 (s, 3H, $CH_3$), 3.64 and 3.69 ($AB_q$, $J$ = 12.5 Hz, 2H, $CH_2$), 3.90 and 3.99 ($AB_q$, $J$ = 11.3Hz, 2H, $CH_2$ of benzyl), 7.13-7.64 (m, 9H, $CH_{arom}$). $^{13}C$ NMR($CDCl_3$): $\delta$ = 21.09, 22.26 ($2CH_3$), 47.48, 50.09 ($2CH_2$), 57.78 (C-NH), 128.18, 128.70, 129.20, 130.72, 132.36 (9CH), 72.81, 97.22, 119.68, 136.13, 137.00 (5C), 151.32, 168.36 (2C=N). IR (KBr): $v$ = 3440, 2922, 2852, 2231, 1635, 1515, 1446, 1097, 757, 688 $cm^{-1}$. MS: *m/z* (%); 366 ($M^+$, 20), 330 (12), 275 (16), 211 (24), 196(12), 120(60), 105 (100), 77 (9), 42 (8). Anal.Calcd.for $C_{21}H_{20}ClN_3O$ (365.86): C, 68.94; H, 5.51; N, 11.49%. Found: C, 68.99; H, 5.47; N, 11.44%.

**N–BENZYL–N-{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}AMINE (5E).**

Yellow viscose oil; Yield: 90%; $^{1}$H NMR ($CDCl_3$): $\delta$ = 1.74 (s, 3H, $CH_3$), 2.12 (s,1H, NH), 3.67 and 3.74 ($AB_q$, $J$ = 12.3 Hz, 2H, $CH_2$), 3.91 and 4.01 ($AB_q$, $J$ = 11.3 Hz, 2H, $CH_2$ of benzyl), 7.27-7.65 (m, 10H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 22.30 ($CH_3$), 47.74, 50.09 ($2CH_2$), 57.80 (C-NH), 127.36, 128.23, 128.53, 128.71, 130.75, 132.37 (10CH), 73.56, 95.04, 119.65, 139.18 (4C), 151.35, 168.30 (2C=N). IR (KBr): $v$ = 3441, 2923, 2852, 2231, 1636, 1540, 1496, 758, 737, 689 cm$^{-1}$. MS: *m/z* (%); 352 ($M^+$, 40), 316 (56), 261 (36), 211(12), 182 (20), 129 (12), 106 (24), 91 (100), 65 (9), 42 (9). Anal.Calcd.for $C_{20}H_{18}ClN_3O$ (351.83): C, 68.28; H, 5.16; N, 11.94%. Found: C, 68.23; H, 5.21; N, 11.89%.



**N–BENZYL–N-{2–CHLORO–1–(CHLOROMETHYL)–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}AMINE (5F).**

Yellow powder; yield: 85%; m.p. 43-45 ºC; $^{1}$H NMR ($CDCl_3$): $\delta$ = 2.12 (s, 1H, NH), 3.64 (s, 2H, $CH_2$ of benzyl), 4.17 (s, 4H, $2CH_2$), 7.30-7.89 (m, 10H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 44.34 ($2CH_2$), 47.53 ($CH_2$ of benzyl), 61.60 (C-NH), 127.60, 128.26, 128.56, 128.74, 130.88, 132.41 (10CH), 73.55, 100.00, 119.58, 138.25, (4C), 164.87, 169.98 (2C=N). IR (KBr): $v$ = 3284, 2910, 2827, 2235, 1608, 1437, 1144, 781, 686 cm$^{-1}$. Anal.Calcd.for $C_{20}H_{17}Cl_2N_3O$ (386.27): C, 62.19; H, 4.44; N, 10.88%. Found: C, 62.13; H, 4.50; N, 10.82%.

**N-{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(2-FURYLMETHYL)AMINE (5G).**

Yellow viscose oil; yield: 90%; $^1$H NMR ($CDCl_3$): $\delta$ = 1.73 (s, 3H, $CH_3$), 2.14 (s, 1H, NH), 3.74 and 3.82 ($AB_q$, $J$ = 13.7 Hz, 2H, $CH_2$), 3.88 and 3.96 ($AB_q$, $J$ = 11.3 Hz, 2H, $CH_2$ of benzyl ,), 6.13 (d, $J$ = 2.7 Hz, 1H, CH of furfuryl), 6.27 (m, 1H, CH of furfuryl), 7.33 (m, 1H, CH of furfuryl), 7.39-7.64 (m, 5H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 21.96 ($CH_3$), 40.47, 50.01 ($2CH_2$), 57.34 (C-NH), 107.38, 110.32, 128.71, 130.74, 132.36, 142.16 (8CH), 72.76, 97.27, 119.65, 151.36 (4C), 152.30, 168.02 (2C=N). IR (KBr): $\nu$ = 3426, 2923, 2225, 1650, 1539, 1442, 1150, 750, 688 cm$^{-1}$. Anal.Calcd.for $C_{18}H_{16}ClN_3O_2$ (341.79): C, 63.25; H, 4.72; N, 12.29%. Found: C, 63.20; H, 4.77; N, 12.24%.



**N-{2–CHLORO–1–(CHLOROMETHYL)–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(4-METHYLBENZYL)AMINE (5H).**

Yellow powder; yield: 87%; m.p. 72-74 ºC; $^1$H NMR ($CDCl_3$): $\delta$ = 2.07 (s, 1H, NH), 2.30 (s, 3H, $CH_3$), 3.59 (s, 2H, $CH_2$ of benzyl), 4.15 (s, 4H, $2CH_2$), 7.12-7.65 (m, 9H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 21.09 ($CH_3$), 44.34 ($2CH_2$), 47.27 ($CH_2$ of benzyl), 61.55 (C-NH), 128.22, 128.73, 129.21, 130.86, 132.40 (9CH), 73.86, 87.45, 128.80, 135.23, 137.30 (5C), 165.76, 177.03 (2C=N). IR (KBr): $\nu$ = 3265, 3976, 2897, 2237, 1551, 1535, 1439, 1109, 805, 773, 685 cm$^{-1}$. Anal.Calcd.for $C_{21}H_{19}Cl_2N_3O$ (400.30): C, 63.01; H, 4.78; N, 10.50%. Found: C, 63.07; H, 4.72; N 10.44%.

**N-{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(4-FLUOROBENZYL)AMINE (5I).**

Yellow viscose oil; yield: 85%; $^1$H NMR ($CDCl_3$): $\delta$ = 1.72 (s, 3H, $CH_3$), 2.07 (s, 1H, NH), 3.64 and 3.72 ($AB_q$, $J$ = 12.3 Hz, 2H, $CH_2$), 3.85 and 3.95 ($AB_q$, $J$ = 11.5 Hz, 2H,

$CH_2$ of benzyl), 6.96-7.65 (m, 9H, $CH_{arom}$). $^{13}C$ NMR($CDCl_3$): $\delta$ = 22.34 ($CH_3$), 46.97, 50.07 ($2CH_2$), 57.74 (C-NH), 115.31 (2CH, d, $^2J_{CF}$ = 21.3 Hz), 128.71, 130.78, 132.37(5CH), 129.82 (2CH, d, $^3J_{CF}$ = 7.5 Hz ), 72.71, 97.37, 119.60, 135.00 (4C), 159.25 (1C, d, $^1J_{CF}$ = 220.16 Hz), 168.19, 151.37 (2C=N). IR (KBr): $\nu$ = 3456, 3269, 2927, 1608, 1449, 1069 $cm^{-1}$. Anal.Calcd for $C_{20}H_{17}ClFN_3O$ (369.82): C, 64.95; H, 4.63; N, 11.36%. Found: C, 64.90; H, 4.68; N, 11.41%.



**N-{2–CHLORO–1–(CHLOROMETHYL)–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(1-NAPHTHYLMETHYL)AMINE (5J).**

Yellow powder; yield: 88%; m.p. 90-92 ºC; $^1H$ NMR ($CDCl_3$): $\delta$ = 2.14 (s, 1H, NH), 4.07 (s, 2H, $CH_2$ of benzyl), 4.22 (s, 4H, $2CH_2$), 7.24-8.07 (m, 12H, $CH_{arom}$). $^{13}C$ NMR($CDCl_3$): $\delta$ = 44.30 ($2CH_2$), 45.98 ($CH_2$ of benzyl), 61.83 (C-NH), 125.39, 126.38, 126.98, 128.59, 128.73, 128.75, 130.92, 132.43, 133.85 (12CH), 72.07, 94.36, 119.85, 123.87, 125.89, 136.28 (6C), 165.32, 166.16 (2C=N). IR (KBr): $\nu$ = 3277, 2922, 2850, 2234, 1542, 1436, 1103, 731, 687 $cm^{-1}$. Anal.Calcd.for $C_{24}H_{19}Cl_2N_3O$ (436.33): C, 66.06; H, 4.39; N, 9.63%. Found: C, 66.11; H, 4.34; N, 9.58%.

**N-{2,2–DICHLORO–1-METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}-N–(4- METHOXYBENZYL)AMINE (5K).**

Yellow viscose oil; yield: 84%; $^1H$ NMR ($CDCl_3$): $\delta$ = 1.90 (s, 3H, $CH_3$), 2.27 (s, 1H, NH), 3.62 and 3.76 ($AB_q$, $J$ = 12.3 Hz, 2H, $CH_2$ of benzyl), 3.77(s, 3H, $OCH_3$), 6.21 (s, 1H, CH), 6.85 (d, $J$ = 8.5 Hz, 2H, $CH_{arom}$), 7.21 (d, $J$ = 8.5 Hz, 2H, $CH_{arom}$), 7.40- 7.66 (m, 5H, $CH_{arom}$). $^{13}C$ NMR($CDCl_3$): $\delta$ = 18.79 ($CH_3$), 47.21 ($CH_2$), 51.08 (C-NH), 56.66

($OCH_3$), 63.37 (CH), 113.93, 128.71, 129.37, 130.80, 132.39 (9CH), 78.76, 93.34, 128.55, 130.90, 161.08 (5C), 165.43, 166.37 (2C=N). IR (KBr): $\nu$ = 3455, 2924, 2231, 1612, 1512, 1247, 757 $cm^{-1}$. Anal.Calcd.for $C_{21}H_{19}Cl_2N_3O_2$ (416.30): C, 60.59; H, 4.60; N, 10.09%. Found: C, 60.54; H, 4.55; N, 10.04%.

**N-(2–CHLOROBENZYL)–N–{2-CHLORO-1-METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}AMINE (5L).**

Yellow powder; yield: 94%; m.p. 56-58 ºC; $^1$H NMR ($CDCl_3$): $\delta$ = 1.76 (s, 3H, $CH_3$), 2.29 (s, 1H, NH), 3.79 and 3.86 ($AB_q$, $J$ =13.0 Hz, 2H, $CH_2$), 3.93 and 4.01 ($AB_q$, $J$ = 11.3 Hz, 2H, $CH_2$ of benzyl), 7.16-7.65 (m, 9H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 22.32 ($CH_3$), 45.74, 50.12 ($2CH_2$), 57.82 (C-NH), 127.03, 128.70, 128.85, 129.56, 130.27, 130.73, 132.37 (9CH), 72.56, 97.24, 119.55, 133.69, 136.58 (4C), 168.35, 172.15 (2C=N). IR (KBr): $\nu$ = 3286, 2969, 2921, 2224, 1600, 1545, 1459, 1129, 763, 691 $cm^{-1}$. Anal.Calcd.for $C_{20}H_{17}Cl_2N_3O$ (386.27): C, 62.19; H, 4.44; N, 10.88%. Found: C, 62.15; H, 4.48; N, 10.92%.

**N-{2–CHLORO–1–(CHLOROMETHYL)–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(2-FURYLMETHYL)AMINE (5M).**

Yellow viscose oil; yield: 88%; $^1$H NMR ($CDCl_3$): $\delta$ = 1.87 (s,1H, NH), 3.73 (s, 2H, $CH_2$ of benzyl), 4.15 (s, 4H, $2CH_2$), 6.10 (d, $J$ = 2.7 Hz, 1H, CH of furfuryl), 6.26 (m, 1H, CH of furfuryl), 7.33 (m,1H, CH of furfuryl), 7.40-7.65 (m, 5H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 40.28 ($CH_2$ of benzyl), 44.19 ($2CH_2$), 61.23 (C-NH), 107.77, 110.40, 128.74, 130.20, 132.40, 142.37 (8CH), 78.32, 93.16, 120.05, 157.27 (4C), 165.42, 166.12

(2C=N). IR (KBr): $\nu$ = 3439, 2924, 2853, 2232, 1633, 1540, 1441, 1147, 740, 688 $cm^{-1}$. Anal.Calcd.for $C_{18}H_{15}Cl_2N_3O_2$ (376.24): C, 57.46; H, 4.02; N, 11.17%. Found: C, 57.40; H, 4.08; N, 11.11%.

**N–BENZYL–N-{2,2–DICHLORO–1-METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}AMINE (5N).**

Yellow viscose oil; yield: 82%; $^1$H NMR ($CDCl_3$): $\delta$ = 1.93 (s, 3H, $CH_3$), 2.16 (s, 1H, NH), 4.50 and 3.54 ($AB_q$, $J$ = 9.5 Hz, 2H, $CH_2$ of benzyl), 6.06 (s, 1H, CH), 7.04-8.45 (m, 10H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 22.20 ($CH_3$), 52.04 ($CH_2$), 58.46 (C-NH), 68.23 (CH), 128.71, 130.81, 132.41, (10CH), 86.52, 93.11, 119.95, 143.48 (4C), 152.88, 163.97 (2C=N). IR (KBr): $\nu$ = 3440, 3134, 2907, 2232, 1645, 1507, 1445, 1099, 756, 685 $cm^{-1}$. Anal.Calcd.for $C_{20}H_{17}Cl_2N_3O$ (386.27): C, 62.19; H, 4.44; N, 10.88%. Found: C, 62.13; H, 4.50; N, 10.82%.

**N-(2–CHLOROBENZYL)–N-{2-CHLORO-1–(CHLOROMETHYL)–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}AMINE (5O).**

Yellow powder; yield: 94%; m.p. 60-62 ºC; $^1$H NMR ($CDCl_3$): $\delta$ = 2.25 (s, 1H, NH), 3.76 (s, 2H, $CH_2$ of benzyl), 4.18 (s, 4H, $2CH_2$), 7.21-7.65 (m, 9H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 44.26 ($2CH_2$), 45.04 ($CH_2$ of benzyl), 61.58 (C-NH), 127.10, 128.74, 129.05, 129.64, 130.43, 132.43, 135.70 (9CH), 73.82, 90.06, 119.49, 130.89, 133.73 (5C), 158.22, 164.70 (2C=N). IR (KBr): $\nu$ = 3280, 2983, 2851, 2233, 1541, 1473, 1144, 752, 686 $cm^{-1}$. Anal.Calcd.for $C_{20}H_{16}Cl_3N_3O$ (420.72): C, 57.10; H, 3.83; N, 9.99%. Found: C, 57.16; H, 3.77; N, 9.93%.

**N-{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(3,4-DICHLOROBENZYL)AMINE (5P).**

Yellow powder; yield: 86%; m.p. 58-60 ºC; $^{1}$H NMR ($CDCl_3$): $\delta$ = 1.70 (s, 3H, $CH_3$), 2.06 (s, 1H, NH), 3.64 and 3.75 ($AB_q$, $J$ = 13.0 Hz, 2H, $CH_2$), 3.89 and 4.01 ($AB_q$, $J$ = 11.5 Hz, 2H, $CH_2$ of benzyl), 7.14-7.64 (m, 8H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 22.37 ($CH_3$), 46.52, 50.09 ($2CH_2$), 57.73 (C-NH), 127.46, 128.72, 130.05, 130.36, 130.82, 132.39 (8CH), 72.61, 97.51, 119.55, 131.19, 132.46, 139.71 (6C), 151.40, 167.96 (2C=N). IR (KBr): $\nu$ = 3321, 3969, 2887, 2230, 1538, 1467, 1102, 751, 682 cm$^{-1}$. Anal.Calcd.for $C_{20}H_{16}Cl_3N_3O$ (420.72): C, 57.10; H, 3.83; N, 9.99%. Found: C, 57.15; H, 3.88; N, 9.94%.

**N-{2,2–DICHLORO–1-METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}-N–(4-METHYLBENZYL)AMINE (5Q).**

Yellow viscose oil; yield: 83%; $^{1}$H NMR ($CDCl_3$): $\delta$ = 1.89 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 2.31 (s,1H, NH), 3.65 and 3.78 ($AB_q$, $J$ = 12.3 Hz, 2H, $CH_2$ of benzyl), 6.21 (s, 1H, CH), 7.10- 7.76 (m, 9H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 21.19, 18.00 ($2CH_3$), 47.56 ($CH_2$), 58.68 (C-NH), 63.46 (CH), 128.10, 128.71, 129.21, 130.92, 132.39 (9CH), 87.76, 95.44, 125.25, 137.03, 146.03 (5C), 162.23, 165.57 (2C=N). IR (KBr): $\nu$ = 3440, 2922, 2854, 2223, 1709, 1539, 1443, 1098, 803, 756, 688 cm$^{-1}$. Anal.Calcd.for $C_{21}H_{19}Cl_2N_3O$ (400.30): C, 63.01; H, 4.78; N, 10.50%. Found: C, 63.06; H, 4.73; N, 10.55%.

**N–{2–CHLORO–1–METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}–N-(1-NAPHTHYLMETHYL)AMINE (5R).**

Yellow powder; Yield: 86%; m.p. 74-76 ºC; $^{1}$H NMR ($CDCl_3$): $\delta$ = 1.83 (s, 3H, $CH_3$), 2.14 (s,1H, NH), 3.97 and 4.09 ($AB_q$, $J$ = 11.3 Hz, 2H, $CH_2$), 4.13 and 4.19 ($AB_q$, $J$ = 11.7 Hz, 2H, $CH_2$ of benzyl), 7.39-8.12 (m, 12H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 22.28 ($CH_3$), 45.49, 50.01 ($2CH_2$), 57.96 (C-NH), 123.74, 125.48, 125.79, 126.31, 126.75, 128.32, 128.51, 128.74, 130.78, 132.39 (12CH), 72.77, 92.54, 119.65, 131.72, 133.86, 134.66 (6C), 151.40, 168.32 (2C=N). IR (KBr): $\nu$ = 3273, 2962, 2850, 2230, 1540, 1636, 1481, 1093, 755, 702 cm$^{-1}$. Anal.Calcd.for $C_{24}H_{20}ClN_3O$ (401.89): C, 71.73; H, 5.02; N, 10.46%. Found: C, 71.79; H, 5.08; N, 10.40%.

**N-ALLYL-N-{2,2–DICHLORO–1-METHYL–1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}AMINE (5S).**

Yellow viscose oil; yield: 82%; $^{1}$H NMR ($CDCl_3$): $\delta$ = 1.85 (s, 3H, $CH_3$), 2.17 (s,1H, NH), 3.17 and 3.27 ($AB_q$, $J$ =13.2 Hz, 2H, $CH_2$ of allyl), 5.15 (m, 2H, $=CH_2$), 5.82 (m, 1H, =CH), 6.16 (s, 1H, CH), 7.39- 7.65 (m, 5H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 31.02 ($CH_3$), 47.86 ($CH_2$), 53.32 (C-NH), 71.16 (CH), 128.63, 128.71, 132.39, 135.82 (6CH), 117.56 ($CH_2$), 75.06, 96.35, 117.23 (3C), 165.23, 168.87 (2C=N). IR (KBr): $\nu$ = 3456, 3924, 2852, 2232, 1644, 1539, 1443, 1095, 757, 687 cm$^{-1}$. Anal.Calcd.for $C_{16}H_{15}Cl_2N_3O$ (336.22): C, 57.16; H, 4.50; N, 12.50%. Found: C, 57.11; H, 4.55; N, 12.45%.

**N-ALLYL-N-{2–CHLORO-1-(CHLOROMETHYL)-1-[5–(2-PHENYL-1-ETHYNYL)-1,3,4-OXADIAZOL–2–YL]ETHYL}AMINE (5T).**

Yellow viscose oil; yield: 87%; $^{1}$H NMR ($CDCl_3$): $\delta$ = 1.82 (s, 1H, NH), 3.12 (d, 2H, $CH_2$ of benzyl), 4.12 (s, 4H, $2CH_2$), 5.12 (m, 2H, $=CH_2$), 5.80 (m, 1H, =CH), 7.40-7.65 (m, 5H, $CH_{arom}$). $^{13}$C NMR($CDCl_3$): $\delta$ = 44.34 ($2CH_2$), 46.01 ($CH_2$ of benzyl), 61.42 (C-NH), 128.74, 130.89, 132.41, 134.86 (6CH), 117.24 ($CH_2$), 82.36, 97.89, 119.47 (3C), 162.22, 164.85 (2C=N). IR (KBr): $v$ = 3440, 2924, 2852, 2232, 1644, 1539, 1440, 1147, 755, 688 $cm^{-1}$. Anal.Calcd.for $C_{16}H_{15}Cl_2N_3O$ (336.22): C, 57.16; H, 4.50; N, 12.50%. Found: C, 57.11; H, 4.55; N, 12.45%.

For complete experimental and spectral details, please see the Supplementary Information, available online.



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## REFERENCES

1. Zhu, J.; Bienayme, H. Multicomponent Reactions. Eds. Wiley. Weinheim. **2005**.

2. Henkel, B.; Sax, M.; Dömling, A. A new and efficient multicomponent solid-phase synthesis of 2-acylaminomethylthiazoles. *Tetrahedron Letters*. **2003**, *44*, 3679–3682.

3. Waller, R. W.; Diorazio, L. J.; Taylor, B. A.; Motherwell, W. B.; Sheppard, T. D. Isocyanide based multicomponent reactions of oxazolidines and related systems. *Tetrahedron*. **2010**, *66*, 6496-6507.

4. Yavari, I.; Hossaini, Z.; Sabbaghan, M. Synthesis of functionalized 5-imino-2,5-dihydro-furans through the reaction of isocyanides with activated acetylenes in the presence of ethyl bromopyruvate. *Mol Divers.* **2006**, *10*, 479-482.

5. Yavari, I.; Bayat, M. J.; Sirouspour, M.; Souri, S. One-pot synthesis of highly functionalized 1,2-dihydropyridines from primary alkylamines, alkyl isocyanides, and acetylenic esters. *Tetrahedron*. **2010**, *66*, 7995-7999.

6. Bayat, M.; Imanieh, H.; Zabarjad Shiraz, N.; Shah Qavidel, M. One-pot, three-component reaction of isocyanides, dialkyl acetylenedicarboxylates, and non-cyclic anhydrides: synthesis of 2,5-diaminofuran derivatives and dialkyl (E)-2-[(N-acyl-N-alkylamino)carbonyl]-2-butenedioates. *Monatsh Chem*. **2010**, *141*, 333–338

7. Ramazani, A.; Ahmadi, Y.; Mahyari, A. One-Pot Efficient Synthesis of Fully Substituted 1,3,4-Oxadiazole Derivatives from (N-Isocyanimino)triphenylphosphorane, Carboxylic Acids, and Aromatic Bis-Aldehydes. *Synthetic Communications*. **2011**, *41*, 2273-2282.

8. Venkata, S. R. C.; Vedula Rajeswar, R. Synthesis of coumarin-substituted thiazolyl-pyrazolone derivatives via one-pot reaction. *Journal of Sulfur Chemistry*. **2010**, *31*, 545-550.

9. Ramazani, A.; Mahyari, T. A.; Rouhani, M.; Rezaei, A. A novel three-component reaction of a secondary amine and a 2-hydroxybenzaldehyde derivative with an isocyanide in the presence of silica gel: An efficient one-pot synthesis of benzo[b]furan derivatives.*Tetrahedron Lett* . **2009**, *50*, 5625- 5627.

10. Domling, A.; Recent developments in isocyanide based multicomponent reactions in applied chemistry.*Chem Rev.* **2006**, *106*, 17-89.

11. Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew Chem Int Ed Engl*. **2000**, 39, 3168-3210.

12. Ugi, I.; Werner,B.; Dömling, A. The chemistry of isocyanides, their multicomponent reactions and their libraries. *Molecules.* **2003***, 8*, 53-66.

13. Dömling, A.; Herdtweck, E.; Heck, S. Cyanamide in isocyanide-based MCRs. *Tetrahedron Letters*. **2006**, *47*, 1745-1747.

14. Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, JM. Synthetic applications of intramolecular aza-Wittig reaction for the preparation of heterocyclic compounds. *Curr Org Chem.* **2009**, *13*, 810-828.

15. Palacios, F.; Retana, O.; Marigorta, E.; Rodriguez, M.; Pagalday, J. Aza-Wittig reaction of N-phosphorylalkyl phosphazenes with carbonyl compounds and phenylisocyanate. Synthesis of 4-amino-3-phosphoryl-2-azadienes and pyrazine-phosphonates. *Tetrahedron*. **2003**, *59*, 2617-2623.

16. Huang, N.; Liang, Y.; Ding, M.; Fu, L.; He, H.; Efficient synthesis and biological evaluation of 1,2,9-trisubstituted 1,9-dihydro-6H-purin-6-ones. *Bioorganic & Medicinal Chemistry Letters*. **2009**, *19*, 831-833.

17. Stolzenberg, H.; Weinberger, B.; Fehlhammer,WP.; Pühlhofer, FG.; Weiss, R. Free and metal-coordinated (N-isocyanimino)triphenylphosphorane: X-ray structures and selected reactions. *Eur J Inorg Chem.* **2005**, *21*, 4263-4271.

18. Ramazani, A.; Bodaghi , A.; One-pot, four-component synthesis of dialkyl [indane-1,3-dione-2-ylidene]alkoxysuccinates. *Tetrahedron Lett.* **2000**, *41*, 567- 568.

19. Pakravan, P.; Ramazani, A.; Noshiranzadeh, N.; Sedrpoushan, A. One-pot synthesis of fluorine-containing alkenes from in situ-generated stabilized phosphorus ylides. *Phosphorus, Sulfur. Silicon Relat. Elem.* **2007**, *182*, 545-549.

20. Ramazani, A.; Rahimifard, M.; Souldozi, A. Silica-gel-catalyzed stereoselective conversion of stabilized phosphorus ylides to dialkyl (z)-2-(2-methoxycarbonyl-phenoxy)-2-butenedioates in solvent-free conditions. *Phosphorus, Sulfur. Silicon Relat. Elem*. **2007***, 182*, 1-5.

21. Ramazani, A .; Rahimifard, M.; Noshiranzadeh, N.; Souldozi, A . Dipotassium hydrogen phosphate–catalyzed synthesis of dialkyl 2-(4-fluoro-phenoxy)-2-butendioates from stabilized phosphorus ylides in solvent-free conditions. *Phosphorus, Sulfur. Silicon Relat. Elem*. **2007**, *182*, 413-417.

22. Ramazani, A.; Ahmadi, E.; Kazemizadeh, A. R.; Dolatyari, L.; Noshiranzadeh, N.; Eskandari, I.; Souldozi, A. One-pot, three-component synthesis of dialkyl 1,2-dihydro quinoline-2,3-dicarboxylates from triphenylphosphine, acetylenic esters, and amide derivatives of 2-aminobenzaldehyde in aqueous acetone. *Phosphorus, Sulphur, Silicon Relat. Elem.* **2005**, *180*, 2419-2422.

23. Ramazani, A.; Mohammadi-Vala, M. A. Facile synthetic approach to sterically congested phosphorus ylides from acetylenic esters, CH-acids, and triphenylphosphine. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2001**, *176*, 223-229.

24. Ramazani, A.; Amini, I.; Massoudi, A. Dipotassium hydrogen phosphate powder–catalyzed stereoselective synthesis of N-vinyl pyrazoles in solvent-free conditions. *Phosphorus, Sulfur. Silicon Relat. Elem.* **2006**, *181*, 2225-2229.

25. Holla, B. S.; Gonsalves, R.; Shenoy, S. Synthesis and antibacterial studies of a new series of 1,2-bis(1,3,4-oxadiazol-2-yl)ethanes and 1,2-bis(4-amino-1,2,4-triazol-3-yl)ethanes.*Eur. J. Med. Chem.* **2000**, *35*, 267-271.

26. Chen, Q.; Zhu, X. H.; Jiang, L. L.; Liu, Z. M.; Yang, G. F. Synthesis, antifungal activity, and CoMFA analysis of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives. *Eur. J. Med. Chem.* **2008**, *43*, 595-603.

27. Amir, M.; Shikha, K. Synthesis and anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino)phenyl]acetic acid derivatives. *Eur. J. Med. Chem*. **2004**, 39, 535-545.

28. Baxendale, I. R.; Ley, S. V.; Martinelli, M. The rapid preparation of 2-aminosulfonamide-1,3,4-oxadiazoles using polymer-supported reagents and microwave heating. *Tetrahedron.* **2005**, *61*, 5323-5349.

29. Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. Efficient one-pot preparation of 5-substituted-2-amino-1,3,4-oxadiazoles using resin-bound reagents. *Tetrahedron Lett*. **2004**, *45*, 3257-3260.

30. Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. Novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using polymer-supported Burgess reagent under microwave conditions. *Tetrahedron Lett* . **1999**, *40*, 3275-3278.

31. Wang, Y.; Sauer, D. R.; Djuric, S. W. A simple and efficient one step synthesis of 1,3,4-oxadiazoles utilizing polymer-supported reagents and microwave heating. *Tetrahedron Lett.* **2006**, *47*, 105-108.

32. Souldozi, A.; Ramazani, A.; Bouslimani, N.; Welter, R. The reaction of (N-isocyanimino)triphenylphosphorane with dialkyl acetylenedicarboxylates in the presence

of 1,3- diphenyl-1,3-propanedione: A novel three-component reaction for the stereoselective synthesis of dialkyl (Z)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates. *Tetrahedron Lett.* **2007**, *48*, 2617-2620.

33. Souldozi, A.; Ramazani, A. The reaction of (N-isocyanimino)triphenylphosphorane with benzoic acid derivatives: A novel synthesis of 2-aryl-1,3,4-oxadiazole derivatives.*Tetrahedron Lett*. **2007**, *48*, 1549-1551.

34. Souldozi, A.; Ramazani, A. (N-Isocyanimino)triphenylphosphorane as an efficient reagent for the synthesis of 1,3,4-oxadiazoles from 3-substituted benzoic acid derivatives. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2009**, *184*, 3191-3198.

35. Souldozi, A.; Ramazani, A. The reaction of (N-isocyanimino)triphenylphosphorane with anthranilic acid derivatives: One-pot synthesis of 2-substituted 1,3,4-oxadiazoles via intramolecular aza-Wittig reaction. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2009**, *184*, 2344-2350.

36. Souldozi, A.; Ramazani, A. Iminophosphorane-mediated one-pot synthesis of 1,3,4-oxadiazole derivatives. *Arkivoc.* **2008**, *16*, 235-242.

37. Souldozi, A.; Ślepokura, K.; Lis, T.; Ramazani, A. Synthesis and single-crystal x-ray structure of 2-(1,3,4-oxadiazol-2-yl)aniline.*Z. Naturforsch*. **2007**, *62b*, 835-840.

38. Ramazani, A.; Rezaei, A. Novel one-pot, four-component condensation reaction: An efficient approach for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives by a Ugi-4CR/aza-Wittig sequence.*Org. Lett*. **2010**, *12*, 2852-2855.

39. Ramazani, A.; Ahmadi, Y.; Rouhani, M.; Shajari, N.; Souldozi, A. The reaction of (Nisocyanimino) triphenylphosphorane with an electron-poor α-haloketone in the presence of aromatic carboxylic acids: A novel three-component reaction for the

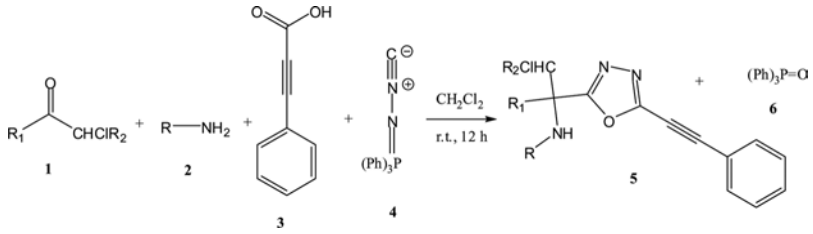
synthesis of disubstituted 1,3,4-oxadiazole derivatives. *Heteroatom Chemistry.* **2010**, *21*, 368-372.

40. Ramazani, A.; Zeinali Nasrabadi, F.; Mashhadi Malekzadeh, A.; Ahmadi, Y. Synthesis of sterically congested 1,3,4-oxadiazole derivatives from aromatic carboxylic acids, acenaphthoquinone, and (N-isocyanimino)triphenylphosphorane*Monatsh Chem*. **2011**, *142*, 625-630.

41. Ramazani, A.; Ahmadi, Y.; Zeinali Nasrabadi, F. *Z.* Four-component Synthesis of 1,3,4-Oxadiazole Derivatives from (*N*-Isocyanimino)triphenylphosphorane, (*E*)-Cinnamic Acids, Acetaldehyde and Secondary Amines. *Naturforsch.* **2011**, *66b,* 184-190.

42. Ramazani, A.; Shajari, N.; Mahyari, A.; Ahmadi, Y. A novel four-component reaction for the synthesis of disubstituted 1,3,4-oxadiazole derivatives. *Mol Divers*. **2011**, *15*, 521-527.

Scheme 1. Four-component synthesis of sterically congested 2,5-disubstituted 1,3,4-oxadiazole derivatives **5**.



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