DOI 10.5012/bkcs.2011.32.8.2700

Preparation of Fully Substituted 1,3,4-Oxadiazole Derivatives from *N*-Isocyaniminotriphenylphosphorane, (*E*)-Cinnamic Acids, Chloroacetone and Primary Amines

Ali Ramazani,* Fatemeh Zeinali Nasrabadi, Zahra Karimi, and Morteza Rouhani†

*Chemistry Department, Zanjan University, P. O. Box 45195-313, Zanjan, Iran. *E-mail: aliramazani@gmail.com*
†Young Researchers Club, Zanjan Branch, Islamic Azad University, Zanjan, Iran
Received June 5, 2011, Accepted June 29, 2011

The 1:1 imine intermediate generated by the addition of primary amine to chloroacetone is trapped by *N*-isocyaniminotriphenylphosphorane in the presence of (*E*)-cinnamic acids and the corresponding iminophosphorane intermediate was formed. 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 produced in excellent yields.

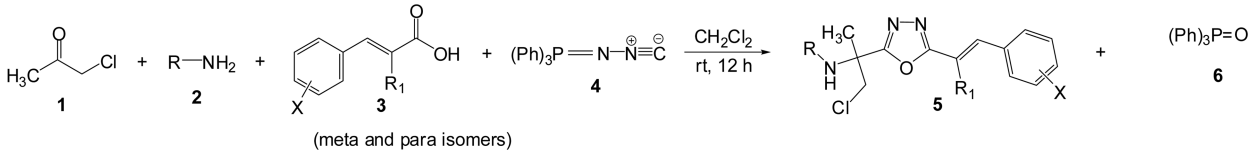
Key Words : *N*-Isocyaniminotriphenylphosphorane, Chloroacetone, (*E*)-Cinnamic acid, 1,3,4-Oxadiazole, *aza*-Wittig reaction

Introduction

Recently, multicomponent condensation reactions (MCRs) have become one of the most powerful methods for the synthesis of small molecule libraries, due to the fact that products are formed in a single step by simultaneous reactions of several reagents and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component.[1-4] This principle, therefore, is highly efficient in terms of time as well as resources.[5] 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 the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.[6]

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.[7] 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.[7] 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. In the last years, several preparative procedures have been reported for the preparations and synthetic applications of iminophosphoranes. *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.[7,8] In recent years, we have established a one-pot method for the preparation of organophosphorus compounds.[9,10]

Since 1,3,4-oxadiazoles are an important class of heterocyclic compounds, they not only have considerable implications in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides but also a wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, and antihypertensive.[11] For the synthesis of 1,3,4-oxadiazole derivatives, several methods have been reported in the literature. It should be mentioned these methods are multi-step in nature.[12,13] The most general method involves the cyclization of diacylhydrazides. This cyclization occurs in the presence of a variety of reagents, such as phosphorous oxychloride, thionyl chloride, or sulfuric acid, usually under harsh reaction conditions. A few reliable and simple methods have been reported for the one-pot



Scheme 1. Four-component synthesis of sterically congested 2,5-disubstituted 1,3,4-oxadiazoles derivatives **5** (see Table 1).

synthesis of 1,3,4-oxadiazoles, especially from available carboxylic acids and acid hydrazides.[14-16] As part of our ongoing program to develop efficient and robust methods for the synthesis of heterocyclic compounds,[17-20] we wish to report the preparation of a new class of 1,3,4-oxadiazole derivatives **5a-o** by a novel Four-component condensation reaction of chloroacetone **1**, primary amine **2**, (*N*-isocyanimino)triphenylphosphorane **4** and (*E*)-cinnamic acids **3** in excellent yields under neutral conditions (Scheme 1).

Experimental

N-Isocyaniminotriphenylphosphorane **4** was prepared based on reported procedures.[8] 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. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{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. 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.

General Procedure for Compounds 5a-o. To a magnetically stirred solution of primary amine derivatives (1 mmol), chloroacetone (0.09 g, 1 mmol), and *N*-isocyaniminotriphenylphosphorane (0.30 g, 1 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of (*E*)-cinnamic acids (1 mmol) in CH_2Cl_2 (5 mL) at room temperature over 15 min. The mixture was stirred at the same temperature for 12 h. The solvent was evaporated 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-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl)-*N*-(4-methylbenzyl) amine (5a):** Yellow viscous oil, yield: 93%. IR (KBr): 3440, 2922, 2853, 1643, 1447, 1091, 764, 694 cm^{-1}; ^{1}H NMR δ 7.09-7.46 (m, 10H, C=CH and CH_{arom}), 3.92 and 4.05 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.62 and 3.70 (AB_q, $^2J_{HH}$ = 12.0 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.16 (s, 1H, NH), 1.73 (s, 3H, CH_3). ^{13}C NMR δ 167.5, 167.2 (2C=N), 136.9, 136.3, 135.4 (3C), 134.6, 129.6, 129.2, 128.5, 128.4, 128.2 (10CH), 121.3 (C), 57.5 (C-NH), 50.2, 47.5 ($2CH_2$), 22.5, 21.1, 14.6 ($3CH_3$). Ms *m/z* (%) 382 (M^+, 36), 346 (32), 291 (32), 225 (72), 196 (16), 120 (32), 105 (100), 91 (12). Anal. Calcd for $C_{22}H_{24}ClN_3O$ (381.90): C 69.19, H 6.33, N 11.00. Found: C 69.24, H 6.28, N 11.05.

***N*-Benzyl-*N*-(2-chloro-1-{5-[(*E*)-2-(3-chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-1-methylethyl)amine (5b):** Yellow viscous oil, yield: 90%. IR (KBr): 3440, 2923, 2852, 1646, 1579, 1165, 742, 699 cm^{-1}; ^{1}H NMR δ 7.27-7.72 (m, 10H, C=CH and CH_{arom}), 7.01 (d, $^3J_{HH}$ = 16.5 Hz, 1H, CH=CH), 3.93 and 4.06 (AB_q, $^2J_{HH}$ = 11.0 Hz, 2H, CH_2 of benzyl), 3.66 and 3.74 (AB_q, $^2J_{HH}$ = 12.2 Hz, 2H, CH_2), 2.16 (s, 1H, NH), 1.74 (s, 3H, CH_3). ^{13}C NMR δ 167.4, 164.4, (2C=N), 139.3 (C), 137.8 (CH), 136.4, 135.1 (2C), 130.3, 130.0, 128.5, 128.2, 127.4, 127.3, 125.6, 111.2 (10CH), 57.6 (C-NH), 47.8, 50.1 ($2CH_2$), 22.5 (CH_3). Ms *m/z* (%) 387 (M^+, 8), 368 (12), 323 (24), 245 (24), 165 (88), 137 (32), 106 (44), 91 (100), 65 (44), 41 (48). Anal. Calcd for $C_{20}H_{19}Cl_2N_3O$ (387.09): C 61.86, H 4.93, N 10.82. Found: C 61.80, H 4.99, N 10.75.

***N*-Benzyl-*N*-(2-chloro-1-methyl-1-{5-[(*E*)-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl)amine (5c):** Yellow powder, yield: 89%, mp 70-72°. IR (KBr): 3444, 2923, 2852, 1644, 1577, 1158, 969, 737, 688 cm^{-1}; ^{1}H NMR δ 7.32-7.56 (m, 11H, C=CH and CH_{arom}), 7.02 (d, $^3J_{HH}$ = 16.5 Hz, 1H, CH=CH), 3.94 and 4.07 (AB_q, $^2J_{HH}$ = 11.5 Hz, 2H, CH_2 of benzyl), 3.66 and 3.74 (AB_q, $^2J_{HH}$ = 12.2 Hz, 2H, CH_2), 2.21 (s, 1H, NH), 1.75 (s, 3H, CH_3). ^{13}C NMR δ 167.2, 164.9 (2C=N), 139.4 (CH), 139.2, 134.6 (2C), 130.1, 129.0, 128.5, 128.2, 127.5, 127.3, 109.8 (11CH), 57.5 (C-NH), 47.8, 50.1 ($2CH_2$), 22.5 (CH_3). Ms *m/z* (%) 354 (M^+, 38), 318 (30), 263 (15), 213 (53), 182 (23), 120 (46), 106 (90), 91 (100), 65 (50), 41 (30). Anal.Calcd for $C_{20}H_{20}ClN_3O$ (353.13): C 67.89, H 5.70, N 11.88. Found: C 67.84, H 5.75, N 11.93.

***N*-(2-Chloro-1-{5-[(*E*)-2-(4-chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-1-methylethyl)-*N*-(4-methoxybenzyl) amine (5d):** Yellow powder, yield: 87%, mp 94-96°. IR (KBr): 3430, 2930, 2835, 1611, 1527, 1463, 1088, 812, 786 cm^{-1}; ^{1}H NMR δ 7.37-7.49 (m, 5H, C=CH and CH_{arom}), 7.22(d, $^3J_{HH}$ = 7.2 Hz, 2H, CH_{arom}), 6.98 (d, $^3J_{HH}$ = 15.0 Hz, 1H, CH=CH), 6.82 (d, $^3J_{HH}$ = 7.0 Hz, 2H, CH_{arom}), 3.91 and 4.04 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.74 (s, 3H, OCH_3), 3.59 and 3.66 (AB_q, $^2J_{HH}$ = 11.5 Hz, 2H, CH_2), 2.07 (s, 1H, NH), 1.73 (s, 3H, CH_3). ^{13}C NMR δ 167.4, 164.6 (2C=N), 158.9 (C), 138.0 (CH), 136.0, 133.1, 131.4 (3C), 129.4, 129.3, 128.7, 113.9, 110.3 (9CH), 57.5 (C-NH), 55.2 (OCH_3), 50.1, 47.2 ($2CH_2$), 22.5 (CH_3). Anal. Calcd for $C_{21}H_{21}Cl_2N_3O_2$ (417.10): C 60.30, H 5.06, N 10.05. Found: C 60.35, H 5.11, N 10.10.

***N*-(2-Chloro-1-{5-[(*E*)-2-(3-chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-1-methylethyl)-*N*-(4-methylbenzyl) amine (5e):** Yellow viscous oil, yield: 85%. IR (KBr): 3434, 2922, 1647, 1527, 1472, 1099, 965, 807, 779 cm^{-1}; ^{1}H NMR δ 7.09-7.53 (m, 9H, C=CH and CH_{arom}), 7.01(d, $^3J_{HH}$ = 16.5 Hz, 1H,CH=CH), 3.92 and 4.04 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.62 and 3.69 (AB_q, $^2J_{HH}$ = 12.5 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.10 (s, 1H, NH), 1.74 (s, 3H, CH_3).^{13}C NMR δ 164.4, 167.5 (2C=N), 137.8, 137.0, 136.4, 136.2 (4C), 135.1, 130.3, 129.9, 129.2, 128.2, 127.4, 125.6, 111.2 (10CH), 57.5 (C-NH), 50.1, 47.5, ($2CH_2$), 22.5, 21.1 ($2CH_3$). Anal. Calcd for $C_{21}H_{21}Cl_2N_3O$ (401.11): C 62.69, H 5.26, N 10.44. Found: C 62.65, H 5.21, N 10.49.

***N*-(2-Chlorobenzyl)-*N*-(2-chloro-1-{5-[(*E*)-2-(3-chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-1-methylethyl)amine (5f):**

Yellow powder, yield: 83%, mp 76-78. IR (KBr): 3447, 3269, 2923, 2853, 1651, 1525, 1470, 1094, 885, 755, 680 cm^{-1}; ^1H NMR δ 7.18-7.39 (m, 9H, C=CH and CH_{arom}), 6.99 (d, $^2J_{HH}$ = 16.5 Hz, 1H,CH=CH), 3.94 and 4.04 (AB_q, $^2J_{HH}$ = 11.5 Hz, 2H, CH_2 of benzyl), 3.77 and 3.85 (AB_q, $^2J_{HH}$ = 12.7 Hz, 2H, CH_2), 2.09 (s, 1H, NH), 1.77 (s, 3H, CH_3). ^{13}C NMR δ 167.2, 164.4 (2C=N), 137.8 (CH), 136.6, 136.4, 135.1, 133.7 (4C), 130.4, 130.3, 129.9, 129.5, 128.8, 127.4, 127.0, 125.6, 111.1 (9CH), 57.4 (C-NH), 50.0, 45.3 ($2CH_2$), 22.2 (CH_3). Anal.Calcd for $C_{20}H_{18}Cl_3N_3O$ (422.74): C 56.82, H 4.29, N 9.94. Found: C 56.76, H 4.35, N 9.88.

***N*-(2-Chlorobenzyl)-*N*-(2-chloro-1-methyl-1-{5-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl) amine (5g):** Yellow viscous oil, yield: 84%. IR (KBr): 3430, 2925, 2855, 1645, 1525, 1443, 1091, 750, 694 cm^{-1}; ^1H NMR δ 7.17-7.46 (m, 10H, C=CH and CH_{arom}), 3.93 and 4.08 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.79 and 3.87 (AB_q, $^2J_{HH}$ = 12.7 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.10 (s, 1H, NH), 1.77 (s, 3H, CH_3).^{13}C NMR δ 167.2 (2C=N), 136.7, 135.4 (2C), 134.7 (CH), 133.7 (C), 130.4, 129.6, 129.4, 128.7, 128.5, 128.4, 127.0 (9CH), 121.3 (C), 57.3 (C-NH), 50.1, 45.3 ($2CH_2$), 22.3, 14.6 ($2CH_3$). Anal. Calcd for $C_{21}H_{21}Cl_2N_3O$ (402.32): C 62.69, H 5.26, N 10.44. Found: C 62.74, H 5.21, N 10.49.

***N*-(2-Chloro-1-methyl-1-{5-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl)-*N*-(3,4-dichlorobenzyl) amine (5h):** Yellow viscous oil, yield: 86%. IR (KBr): 3430, 2922, 2850, 1647, 1525, 1448, 1092, 818, 765, 694 cm^{-1}; ^1H NMR δ 7.14-7.53 (m, 9H, C=CH and CH_{arom}), 3.91 and 4.07 (AB_q, $^2J_{HH}$ = 11.5 Hz, 2H, CH_2 of benzyl), 3.64 and 3.76 (AB_q, $^2J_{HH}$ = 13.2 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.08 (s, 1H, NH), 1.71 (s, 3H, CH_3). ^{13}C NMR δ 167.4, 167.1 (2C=N), 139.9, 135.3 (2C), 134.8 (CH), 132.4, 131.1 (2C), 130.3, 130.1, 129.6, 128.5, 128.4, 127.5 (8CH), 121.2(C), 57.4 (C-NH), 46.6, 50.1 ($2CH_2$), 22.6, 14.6 ($2CH_3$). Anal. Calcd for $C_{21}H_{20}Cl_3N_3O$ (436.76): C 57.75, H 4.62, N 9.62. Found: C 57.69, H 4.68, N 9.56.

***N*-(2-Chloro-1-{5-[(*E*)-2-(4-chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-1-methylethyl)-*N*-(4-fluorobenzyl) amine (5i):** Yellow powder, yield: 85%, mp 68-70. IR (KBr): 3440, 2935, 2846, 1647, 1509, 1490, 1087, 968, 816 cm^{-1}; ^1H NMR δ 6.95-7.50 (m, 10H, CH=CH and CH_{arom}), 3.91 and 4.05 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.62 and 3.72 (AB_q, $^2J_{HH}$ = 12.2 Hz , 2H, CH_2), 2.12 (s, 1H, NH), 1.73 (s, 3H, CH_3). ^{13}C NMR δ 167.2, 164.6 (2C=N), 161.8 (d, $^1J_{CF}$ = 283.0 Hz, C), 138.0 (CH), 136.0 (C), 135.1 (d, $^4J_{CF}$ = 3.7 Hz, C), 133.0 (C), 129.8 (d, $^3J_{CF}$ = 8.1 Hz, 2CH), 129.3, 128.7 (4CH), 115.3 (d, $^2J_{CF}$ = 21.3 Hz, 2CH), 110.2 (CH), 57.5 (C-NH), 50.1, 47.0 ($2CH_2$), 22.5 (CH_3). Anal. Calcd for $C_{20}H_{18}Cl_2FN_3O$ (406.28): C 59.13, H 4.47, N 10.34. Found: C 59.18, H 4.52, N 10.39.

***N*-Benzyl-*N*-(2-chloro-1-methyl-1-{5-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl)amine (5j):** Yellow viscous oil, yield: 87%. IR (KBr): 3313, 2931, 2855, 1651, 1545, 1236, 848, 688 cm^{-1}; ^1H NMR δ 7.32-7.79 (m, 11H, C=CH and CH_{arom}), 3.93 and 4.07(AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.66 and 3.75 (AB_q, $^2J_{HH}$ = 12.0 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.11 (s, 1H, NH), 1.74 (s, 3H, CH_3). ^{13}C NMR δ 167.4, 167.3 (2C=N), 139.4, 135.4 (2C), 134.6, 129.6, 128.5, 128.4, 128.3, 127.3 (11CH), 121.3 (C), 57.5 (C-NH), 50.2, 47.8 ($2CH_2$), 22.6, 14.6 ($2CH_3$). Anal. Calcd for $C_{21}H_{22}ClN_3O$ (367.87): C 68.56, H 6.03, N 11.42. Found: C 68.50, H 6.09, N 11.36.

***N*-(2-Chloro-1-methyl-1-{5-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl)-*N*-(2-naphthylmethyl) amine (5k):** Yellow viscous oil, yield: 88%. IR (KBr): 3441, 2925, 2852, 1636, 1525, 1444, 1092, 778, 694 cm^{-1}; ^1H NMR δ 7.37-8.13 (m, 13H, C=CH and CH_{arom}), 4.16 (AB_q, $^2J_{HH}$ = 11.0 Hz, 2H, CH_2 of benzyl), 3.99 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.07 (s, 1H, NH), 1.82 (s, 3H, CH_3). ^{13}C NMR δ 167.5, 167.3 (2C=N), 135.4, 134.9 (2C), 134.7 (CH), 133.9, 131.8 (2C), 129.6, 128.7, 128.5, 128.4, 128.2, 126.8, 126.3, 125.7, 125.5, 123.8 (12CH), 121.2 (C), 57.6 (C-NH), 50.0, 45.6 ($2CH_2$), 14.6, 22.6 ($2CH_3$). Anal.Calcd for $C_{25}H_{24}ClN_3O$ (417.93): C 71.85, H 5.79, N 10.05. Found: C 71.90, H 5.44, N 10.10.

***N*-(2-Chloro-1-methyl-1-{5-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl)-*N*-(4-fluorobenzyl) amine (5l):** Yellow viscous oil, yield: 83%. IR (KBr): 3445, 2924, 2855, 1645, 1509, 1447, 1155, 827, 732, 694 cm^{-1}; ^1H NMR δ 6.94-7.44 (m, 10H, CH=C and CH_{arom}), 3.91 and 4.06 (AB_q, $^2J_{HH}$ = 11.2 Hz , 2H, CH_2 of benzyl), 3.64 and 3.73 (AB_q, $^2J_{HH}$ = 12.2 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.08 (s, 1H, NH), 1.72 (s, 3H, CH_3). ^{13}C NMR δ 167.3 (2C=N), 158.0 (C, d, $^1J_{CF}$ = 251.6 Hz), 135.4 (CH), 135.2, 134.8 (2C), 129.7 (2CH, d, $^3J_{CF}$ = 8.1 Hz), 129.6 (2CH), 128.7 (C), 128.5, 128.4 (3CH), 115.3 (2CH, d, $^2J_{CF}$ = 20.7 Hz), 57.4 (C-NH), 50.2, 47.0 ($2CH_2$), 22.5, 14.6 ($2CH_3$). Anal. Calcd for $C_{21}H_{21}ClFN_3O$ (385.86): C 65.37, H 5.49, N 10.89. Found: C 65.42, H 5.44, N 10.84.

***N*-Benzyl-*N*-(2-chloro-1-{5-[(*E*)-2-(3-methoxyphenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-1-methylethyl)amine (5m):** Yellow viscous oil, yield: 85%. IR (KBr): 3431, 2925, 2853, 1646, 1580, 1454, 1157, 967, 734, 778, 699 cm^{-1}; ^1H NMR δ 6.92-7.70 (m, 11H, CH=CH and CH_{arom}), 4.06 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.84 (s, 3H, OCH_3), 3.74 (AB_q, $^2J_{HH}$ = 11.7 Hz, 2H, CH_2), 2.08 (s, 1H, NH), 1.74 (s, 3H, CH_3). ^{13}C NMR δ 167.8, 161.3 (2C=N), 157.2, 139.9 (2C), 139.3, 136.0, 130.0, 128.6, 128.5, 128.2, 127.1 (9CH), 120.1 (C), 115.7, 112.5 (2CH), 57.6 (C-NH), 55.3 (OCH_3), 50.1, 47.5 ($2CH_2$), 22.9 (CH_3). Anal. Calcd for $C_{21}H_{22}ClN_3O_2$ (383.87): C 65.71, H 5.78, N 10.95. Found: C 65.77, H 5.72, N 10.89.

***N*-(2-Chloro-1-{5-[(*E*)-2-(3-chlorophenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}-1-methylethyl)-*N*-(4-fluorobenzyl) amine (5n):** Yellow viscous oil, yield: 84%. IR (KBr): 3440, 2924, 2855, 1647, 1505, 1429, 1221, 827, 734, 676 cm^{-1}; ^1H NMR δ 6.95-7.72 (m, 10H, CH=CH and CH_{arom}), 3.92 and 4.05 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.63 and 3.72 (AB_q, $^2J_{HH}$ = 12.2 Hz, 2H, CH_2), 2.08 (s, 1H, NH), 1.73(s, 3H, CH_3). ^{13}C NMR δ 167.6, 164.5, (2C=N), 154.5 (d, $^1J_{CF}$ = 188.7 Hz, C), 138.0, 136.4 (2C), 135.1, 130.3 (2CH), 129.9 (d, $^3J_{CF}$ = 5.6 Hz, 2CH), 129.8, 127.4, 125.6 (3CH), 118.7 (C), 111.1 (CH), 115.3 (d, $^2J_{CF}$ = 21.3 Hz, 2CH), 57.5 (C-

NH), 50.1, 47.0 ($2CH_2$), 22.5 (CH_3). Anal. Calcd for $C_{20}H_{18}Cl_2FN_3O$ (406.28): C 59.13, H 4.47, N 10.34. Found: C 59.08, H 4.42, N 10.29.

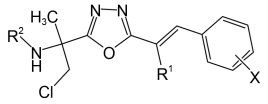
***N*-Benzyl-*N*-(2-chloro-1-methyl-1-{5-[(*E*)-2-(4-methylphenyl) -1-ethenyl]-1,3,4-oxadiazol-2-yl}ethyl)amine (5o):** Yellow viscous oil, yield: 87%. IR (KBr): 3293, 2936, 2857, 1651, 1552, 1453, 1219, 893, 787, 697 cm^{-1}; ^1H NMR δ 7.71 (d, $^3J_{HH}$ = 16.0 Hz, 1H, CH=CH), 7.27-7.51 (m, 9H, CH_{arom}), 6.50 (d, $^3J_{HH}$ = 16.0 Hz, 1H, CH=CH), 3.94 and 4.06 (AB_q, $^2J_{HH}$ = 11.2 Hz, 2H, CH_2 of benzyl), 3.67 and 3.75 (AB_q, $^2J_{HH}$ = 12.2 Hz, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.21 (s, 1H, NH), 1.75 (s, 3H, CH_3). ^{13}C NMR δ 166.8, 165.3 (2C=N), 138.0 (CH), 133.1, 132.8 (2C), 129.4, 129.3, 129.2, 128.7, 128.5 (9CH), 127.4 (C), 110.3 (CH), 57.6 (C-NH), 50.0, 47.8 ($2CH_2$), 26.1, 22.4 ($2CH_3$). Anal. Calcd for $C_{21}H_{22}ClN_3O$ (367.87): C 68.56, H 6.03, N 11.42. Found: C 68.72, H 6.09, N 11.36.

Results and Discussion

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

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 **1**, the next step may involve nucleophilic addition of the *N*-isocyaniminotriphenylphosphorane **4** to the imine intermediate **7**, which facilitates by its protonation with the (*E*)-cinnamic acids **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[17-20] of iminophosphorane moiety with the ester carbonyl to afford the sterically congested 1,3,4-oxadiazole derivatives **5** by removal of triphenylphosphine oxide **6** from intermediate **10**.

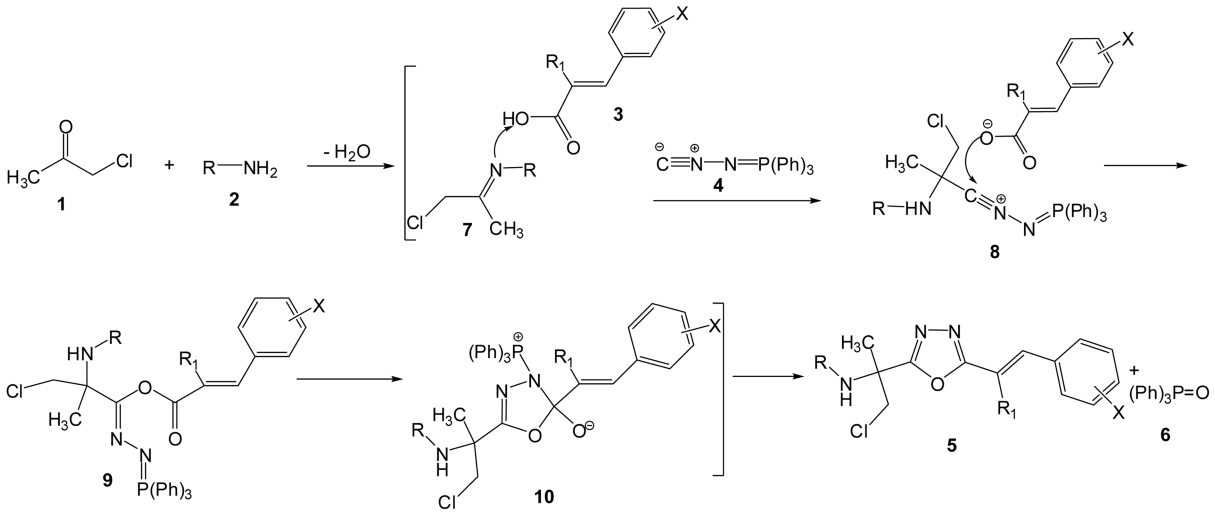
Table 1. Synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives **5a-o** from chloroacetone **1**, primary Amine **2** and (*E*)-cinnamic acids **3** in the presence of *N*-Isocyaniminotriphenylphosphorane **4** (See Scheme 1).



5	R^1	R^2
a	CH_3	4-methylbenzyl
b	H	benzyl
c	H	benzyl
d	H	4-methoxybenzyl
e	H	4-methylbenzyl
f	H	2-chlorobenzyl
g	CH_3	2-chlorobenzyl
h	CH_3	3,4-dichlorobenzyl
i	H	4-fluorobenzyl
j	CH_3	benzyl
k	CH_3	naphthyl
l	CH_3	4-fluorobenzyl
m	H	benzyl
n	H	4-fluorobenzyl
o	H	benzyl

Conclusions

We believe that the reported method offers a mild, simple, and efficient route for the preparation of sterically congested 1,3,4-oxadiazol derivatives **5**. Ease of work-up, high yields and fairly mild reaction conditions make it a useful addition



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

to modern synthetic methodologies. Other aspects of this synthetic process are under investigation.

Acknowledgments. This research was supported by the "Zanjan University" and the "Iran National Science Foundation: INSF".

References

1. Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Eds., Wiley: Weinheim, 2005.
2. Maleki, B.; Gholizadeh, M.; Sepehr, Z. *Bull. Korean Chem. Soc.* **2011**, *32*, 1697.
3. (a) Ramazani, A.; Shajari, N.; Mahyari, A.; Ahmadi, Y. *Mol. Divers*. **2011**, *15*, 521. (b) Ramazani, A.; Rezaei, A.; Mahyari, A. T.; Rouhani, M.; Khoobi, M. *Helv. Chim. Acta.* **2010**, *93*, 2033. (c) Ramazani, A.; Mahyari, A. *Helv. Chim. Acta.* **2010**, *93*, 2203. (d) Ramazani, A.; Mahyari, A. T.; Rouhani, M.; Rezaei, A. *Tetrahedron Lett*. **2009**, *50*, 5625.
4. Zeinali Nasrabadi, F.; Ramazani, A.; Ahmadi, Y. *Mol. Divers*. **2011**, *15*, DOI: 10.1007/s11030-011-9310-9.
5. Domling, A. *Chem. Rev.* **2006**, *106*, 17.
6. Ugi, I.; Werner, B.; Dömling, A. *Molecules*. **2003**, *8*, 53.
7. Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2009**, *13*, 810.
8. Stolzenberg, H.; Weinberger, B.; Fehlhammer, W. P.; Pühlhofer, F. G.; Weiss, R. *Eur. J. Inorg. Chem.* **2005**, *21*, 4263.
9. (a) Ramazani, A.; Bodaghi, A. *Tetrahedron Lett*. **2000**, *41*, 567. (b) Pakravan, P.; Ramazani, A.; Noshiranzadeh, N.; Sedrpoushan, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2007**, *182*, 545. (c) Ramazani, A.; Rahimifard, M.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2007**, *182*, 1.
10. (a) Ramazani, A.; Rahimifard, M.; Noshiranzadeh, N.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2007**, *182*, 413. (b) Ramazani, A.; Ahmadi, E.; Kazemizadeh, A. R.; Dolatyari, L.; Noshiranzadeh, N.; Eskandari, I.; Souldozi, A. *Phosphorus, Sulphur, Silicon Relat. Elem*. **2005**, *180*, 2419. (c) Ramazani, A.; Shajari, N.; Gouranlou, F. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2001**, *174*, 223. (d) Ramazani, A.; Amini, I.; Massoudi, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2006**, *181*, 2225.
11. Holla, B. S.; Gonsalves, R.; Shenoy, S. *Eur. J. Med. Chem*. **2000**, *35*, 267.
12. Chen, Q.; Zhu, X. H.; Jiang, L. L.; Liu, Z. M.; Yang, G. F. *Eur. J. Med. Chem.* **2008**, *47*, 595.
13. Baxendale, I. R.; Ley, S. V.; Martinelli, M. *Tetrahedron.* **2005**, *61*, 5323.
14. Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett*. **2004**, *45*, 3257.
15. Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett*. **1999**, *40*, 3275.
16. Wang, Y.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 105.
17. (a) Souldozi, A.; Ramazani, A.; Bouslimani, N.; Welter, R. *Tetrahedron Lett*. **2007**, *48*, 2617. (b) Souldozi, A.; Ramazani, A. *Tetrahedron Lett*. **2007**, *48*, 1549. (c) Souldozi, A.; Ramazani, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2009**, *184*, 3191.
18. (a) Souldozi, A.; Ramazani, A. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2009**, *184*, 2344. (b) Souldozi, A.; Ramazani, A. *Arkivoc.* **2008**, Xvi, 235. (c) Souldozi, A.; Ślepokura, K.; Lis, T.; Ramazani, A. *Z. Naturforsch*. **2007**, *62b*, 835.
19. (a) Ramazani, A.; Rezaei, A. *Org. Lett*. **2010**, *12*, 2852. (b) Ramazani, A.; Ahmadi, Y.; Rouhani, M.; Shajari, N.; Souldozi, A. *Heteroatom Chem*. **2010**, *21*, 368. (c) Ramazani, A.; Zeinali Nasrabadi, F.; Mashhadi Malekzadeh, A.; Ahmadi, Y. *Monatsh Chem*. **2011**, *142*, 625.
20. (a) Ramazani, A.; Shajari, N.; Tofangchi Mahyari, A.; Khoobi, M.; Ahmadi, Y.; Souldozi, A. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2010**, *185*, 2496. (b) Ramazani, A.; Shajari, N.; Mahyari, A.; Ahmadi, Y. *Mol. Divers* **2011**, *15*, 521.