ICC
Iranian Chemical Communication
Original Research Article
Payame Noor University http://icc.journals.pnu.ac.ir

One-pot, four-component synthesis of fully substituted 1,3,4-oxadiazole derivatives from *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC), a primary amine, a carboxylic acid and cinnamaldehyde

Fatemeh Kalantari[a], Ali Ramazani*[,a] and Fatemeh Zeinali Nasrabadi[b]

[a]*Department of Chemistry, University of Zanjan, P O Box 45195-313 Zanjan, Iran*

[b]*Department of Chemistry, Payame Noor University, P.O. Box 19395-3697 Tehran, Iran*

Received: 23 April 2015, Accepted: 4 October 2015, Published: 4 October 2015

Abstract

The imine intermediate generated by the addition of primary amine to cinnamaldehyde is trapped by *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC) and a carboxylic acid, and leads to the formation of the corresponding iminophosphorane intermediate. 1,3,4-Oxadiazole derivatives are formed *via* intramolecular *aza*-Wittig reaction of the iminophosphorane intermediate. The reactions were completed under neutral conditions at room temperature. The fully substituted 1,3,4-oxadiazole derivatives were produced in high yields. The method offers a mild, simple, and efficient route for the preparation of fully substituted 1,3,4-oxadiazols. The structures of the products were deduced from their IR, ^1H NMR, ^{13}C NMR spectra, and mass spectrometry.Keywords: Baclofen; synthesis; GABA receptor; γ-aminobutiric acid.

Keywords: *N*-Isocyaniminotriphenylphosphorane; cinnamaldehyde; carboxylic acids; 1,3,4-oxadiazole; aza-Wittig reaction.

Introduction

Multicomponent reactions (MCR) have appeared as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atomic economy, straightforward reaction design, and the

*Corresponding author: Ali Ramazani
Tel: +98 (24) 33052572, Fax: +98 (24) 33052477
E-mail: aliramazani@gmail.com

opportunity in order to construct target compounds by the introduction of several diversity elements in a single chemical event. Since all the employed organic reagents are consumed and incorporated into the target compound, purification of products resulting from MCR is also simple [1].

MCRs are flexible reactions for the rapid production of complex molecules with often biologically relevant scaffold structures. Combined with the ease of parallelization and the exploratory power with regard to chemical space, multicomponent reactions have attracted significant attention from the medicinal chemistry community. MCR, leading to interesting heterocyclic scaffolds, are especially useful for the construction of diverse chemical libraries of 'druglike' molecules. The isocyanide-based MCR are very important in this area [2-4]. Among the known multicomponent reactions, 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 atomic efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted considerable attention because of the advantages that they offer to the field of combinatorial chemistry [5-7].

In recent years, there has been considerable investigation on different classes of oxadiazoles. Particularly, compounds containing 1,3,4-oxadiazole nucleus have shown the possession of a wide range of pharmacological and therapeutic activities. Some 1,3,4-oxadiazoles have shown analgesic, anti-inflammatory, anticonvulsant, tranquilizing, myorelaxant, antidepressant, vasodilatatory, diuretic, antiulcer, antiarythmic, antiserotoninic, spasmolytic, hypotensive, antibronchocontrictive, anticholinergic, and antiemetic activities. Additionally, many 1,3,4-oxadiazole derivatives have been reported as active inhibitors of several enzymes[8-11].

Recently, the intramolecular version of the *aza*-Wittig-type reaction has attracted much attention because it has exhibited 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 [4,7]. Existence of 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 [12,13]. However, the organic chemistry of *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC)

4 remains almost unexplored. *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC) **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 [12, 13]. In recent years, we have established a one-pot method for the synthesis of organophosphorus compounds [14-16]. In this paper, we report an interesting four-component reaction of *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC) **4** (Scheme 1).

Experimental

General

N-Isocyaniminotriphenylphosphorane (Ph_3PNNC) **4** was prepared based on reported procedures [13]. 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. ^1H and ^{13}C NMR spectra ($CDCl_3$) were recorded on a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.9MHz, and a BRUKER AVANCE III spectrometer at 400.0 and 100.6 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. Preparative layer chromatography (PLC) plates were prepared from Merck silica gel (F_{254}) powder.

General Procedure for the Preparation of Compounds 5a-5i

To a magnetically stirred solution of primary amine derivatives **2** (1 mmol), cinnamaldehyde **1** (1 mmol) and *N*-isocyaniminotriphenylphosphorane (Ph_3PNNC) **4** (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of carboxylic acid derivatives **3** (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) (silica gel (F_{254}) powder; petroleum ether-ethyl acetate 4:1). The characterization data of the compounds are given below.

***N*-((*E*)-1-{5-[(*E*)-2-(4-Chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-3-phenyl-2-propenyl)- *N*-(4-methylbenzyl)amine (5a)**

Yellow powder (yield 90%), m.p 109-111 °C, ^1H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 2.36 (s, 3H, CH_3), 2.38 (s, 1H, NH), 3.89

(ABq, 2H, $^{2}J_{HH}$ =13.2 Hz, CH_2), 4.84 (d, 1H, $^{3}J_{HH}$ =7.6 Hz, CH), 6.37 (dd, 1H, $^{3}J_{HH}$ =7.6 Hz, $^{3}J_{HH}$ =15.6 Hz, =CH), 6.74 (d, 1H, $^{3}J_{HH}$ =15.6 Hz, =CH), 6.99 (d, 1H, $^{3}J_{HH}$ =16.4 Hz, =CH), 7.07-7.55 (m, 14H,CH_{arom} and =CH). ^{13}C NMR ($CDCl_3$, 100.64 MHz): δ_C (ppm) 21.16 (CH_3), 50.95 (CH_2), 55.92 (CH), 110.39, 125.46, 126.75, 128.33, 128.38, 128.68, 128.72, 129.30, 129.33, 134.25, 137.89 (17 CH), 133.20, 135.85, 135.90, 137.06, 139.33 (5C), 164.59, 166.07 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3414, 3060, 2929, 1680, 1645, 1527, 1348, 1453, 1201, 966, 789, 618. MS: m/z (%) = 441 (M^+, 8), 350 (84), 336 (48), 233(67), 165 (41), 130 (53), 120 (54), 105 (100), 91(80), 77 (60), 65 (42). Anal.Calcd for $C_{27}H_{24}ClN_3O$ (441.16): C, 73.38; H, 5.47; N, 9.51. Found: C, 73.31; H, 5.53; N, 9.56.

_N_-Benzyl-_N_-((_E_)-1-{5-[(_E_)-2-(4-chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-3-phenyl-2-propenyl)amine (5b)

Yellow Viscous oil (yield 82%),^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 2.19 (s, 1H, NH), 3.90 (s, 2H, CH_2), 4.81 (d, 1H, $^{3}J_{HH}$ =7.2 Hz, CH), 6.36 (dd, 1H, $^{3}J_{HH}$ =7.2 Hz, $^{3}J_{HH}$ =16.0 Hz =CH), 6.72 (d, 1H, $^{3}J_{HH}$ =16 Hz, =CH), 6.99 (d, 1H, $^{3}J_{HH}$ =16.5 Hz, =CH), 7.08-7.71 (m, 15H, CH_{arom} and =CH). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C (ppm) 51.20 (CH_2), 55.98 (CH), 110.37, 125.41, 126.71, 127.37, 128.31, 128.37, 128.59, 128.64, 128.68, 129.29, 134.23, 137.87 (18 CH), 133.16, 135.81, 135.90, 139.0 (4C), 164.56, 166.01 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3422, 3061, 2922, 1647, 1527, 1490, 1100, 1012, 815, 698. Anal.Calcd for $C_{26}H_{22}ClN_3O$ (427.93): C, 72.97; H, 5.18; N, 9.82. Found: C, 72.90; H, 5.23; N, 9.90.

_N_-Benzyl-_N_-((_E_)-3-phenyl-1-{5-[(_E_)-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}-2-propenyl)amine (5c)

Yellow Viscous oil (yield 83%),^{1}H NMR ($CDCl_3$, 250 MHz):δ_H (ppm) 2.25 (s, 1H, NH), 3.90 (s, 2H, CH_2), 4.82 (d, 1H, $^{3}J_{HH}$ =7.2 Hz, CH), 6.37 (dd, 1H, $^{3}J_{HH}$ =7.2 Hz, $^{3}J_{HH}$ =16.0 Hz, =CH), 6.72 (d, 1H, $^{3}J_{HH}$ =16.0 Hz, =CH), 7.00 (d, 1H, $^{3}J_{HH}$ =16.2 Hz, =CH), 7.31-7.53 (m, 16H, CH_{arom} and =CH). ^{13}C NMR ($CDCl_3$, 62.9 MHz):δ_C (ppm) 51.20 (CH_2), 55.99 (CH),110.34, 125.36, 126.72, 127.40, 128.34, 128.40, 128.61, 128.67, 128.71, 129.30, 133.13, 134.27, 137.91(19CH), 135.78, 135.88, 138.94 (3C), 164.59, 165.99 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3398, 3028, 2924, 1635, 1602, 1527, 1490, 1453, 1089, 816, 737, 699. Anal.Calcd for $C_{26}H_{23}N_3O$ (393.48): C, 79.36; H, 5.89; N, 10.68. Found: C, 79.30; H, 5.95; N, 10.60.

_N_-Benzyl)-_N_-((_E_)-1-{5-[(_E_)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}-3-phenyl-2-propenyl)amine (5d)

Yellow Viscous oil (yield 87%),^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 2.46 (s, 1H, NH), 2.44 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 4.86 (d, 1H, $^{3}J_{HH}$=7.2 Hz, CH), 6.42 (dd, 1H, $^{3}J_{HH}$ =7.2 Hz, $^{3}J_{HH}$ =16.0 Hz, =CH), 6.75 (d, 1H, $^{3}J_{HH}$ =16.0 Hz, =CH), 7.28-7.54 (m, 16H, CH_{arom} and =CH). ^{13}C NMR ($CDCl_3$, 100.64 MHz): δ_C (ppm) 14.67 (CH_3), 51.25 (CH_2), 56.04 (CH), 125.62, 126.75, 127.39, 128.34, 128.38, 128.54, 128.62, 128.71, 128.94, 129.60, 134.14, 134.65, (18CH), 121.38, 135.52, 135.91, 139.07 (4C), 166.20, 167.32 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3419, 3027, 2922, 1660, 1602, 1531, 1495, 1224, 1159, 968, 823, 738, 697. Anal.Calcd for $C_{27}H_{25}N_3O$ (407.20): C, 79.58; H, 6.18; N, 10.31. Found: C, 79.63; H, 6.11; N, 10.38.

_N_-Benzyl-_N_-((_E_)-1-{5-[(_E_)-2-(4-fluorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-3-phenyl-2-propenyl)amine (5e)

Yellow Viscous oil (yield 80%),^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 2.50 (s, 1H, NH), 3.90 (s, 2H, CH_2), 4.84 (d, 1H, $^{3}J_{HH}$ =7.2 Hz, CH), 6.40 (dd, 1H, $^{3}J_{HH}$ =7.2 Hz, $^{3}J_{HH}$ =16.0 Hz, =CH), 6.75 (d, 1H, $^{3}J_{HH}$ =16.0 Hz, =CH), 6.97 (d, 1H, $^{3}J_{HH}$ =16.4 Hz, =CH), 7.11-7.54 (m, 15H, CH_{arom} and =CH). ^{13}C NMR ($CDCl_3$, 100.64 MHz): δ_C (ppm) 51.23 (CH_2), 56.01 (CH), 109.61, 125.47, 126.74, 127.41, 128.35, 128.38, 128.62, 128.72, 134.25, 138.05 (12CH), 116.22 (d, $^{2}J_{CF}$ =22.1 Hz, $2CH_{arom}$), 129.35 (d, $^{3}J_{CF}$ =8.0 Hz, $2CH_{arom}$), 130.97, 135.85, 139.01 (3C), 174.35 (d, $^{1}J_{CF}$ =301.8 Hz, C_{arom}), 164.71, 165.90 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3419, 3027, 2922, 1650, 1600, 1531, 1453, 1384, 1159, 823, 738, 697. Anal.Calcd for $C_{26}H_{22}FN_3O$ (411.47): C, 75.89; H, 5.39; N, 10.21. Found: C, 75.94; H, 5.34; N, 10.27.

_N_-((_E_)-1-{5-[(_E_)-2-(4-Chlorophenyl)-1-ethenyl]-1,3,4-oxadiazol-2-yl}-3-phenyl-2-propenyl)-_N_-(4-methoxybenzyl)amine (5f)

Yellow Viscous oil (yield 87%),^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 2.33 (s, 1H, NH), 3.79 (s, 3H, OCH_3), 3.83 (s, 2H, CH_2), 4.80 (d, 1H, $^{3}J_{HH}$ =7.5 Hz, CH), 6.36 (dd, 1H, $^{3}J_{HH}$ =7.5 Hz, $^{3}J_{HH}$ =16.0 Hz, =CH), 6.71 (d , 1H, $^{3}J_{HH}$ =16.0 Hz, =CH), 7.10 (d, 1H, $^{3}J_{HH}$ =16.0 Hz, =CH), 6.87, 7.36-7.48 (m,14H, CH_{arom} and =CH). ^{13}CNMR ($CDCl_3$, 62.9 MHz): δ_C (ppm) 50.62 (CH_2), 55.26 (OCH_3), 55.83 (CH), 110.38, 113.96, 125.49, 126.70, 128.33, 128.63, 129.28, 129.55, 134.15, 137.85 (17CH), 131.04, 133.17, 135.83, 135.85, 159.00 (5C), 164.54, 166.06 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3405, 3027, 2931, 1641, 1609, 1512, 1454, 1248, 1176, 1032, 815, 700. Anal.Calcd for $C_{27}H_{24}ClN_3O_2$

(457.95): C, 70.81; H, 5.28; N, 9.18. Found: C, 70.87; H, 5.21; N, 9.24.

_N_-(4-Methoxybenzyl)-_N_-((_E_)-1-{5-[(_E_)-1-methyl-2-phenyl-1-ethenyl]-1,3,4-oxadiazol-2-yl}-3-phenyl-2-propenyl)amine (5g)

Yellow Viscous oil (yield 85%), ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 2.39 (s, 1H, NH), 2.40 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 2H, CH_2), 4.81 (d, 1H, $^3J_{HH}$ =7.25 Hz, CH), 6.37 (dd, 1H, $^3J_{HH}$ =7.25 Hz, $^3J_{HH}$ =16.0 Hz, =CH), 6.71 (d, 1H, $^3J_{HH}$ =16.0 Hz, =CH), 6.86-7.50 (m, 15H, CH_{arom} and =CH). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C (ppm) 14.61 (CH_3), 50.65 (CH_2), 55.27 (OCH_3), 55.86 (CH), 113.94, 125.71, 126.70, 128.25, 128.31, 128.49, 128.66, 129.56, 133.98, 134.56 (17CH), 121.37, 131.14, 135.50, 135.92, 158.91 (5C), 166.22, 167.00 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3383, 2900, 1667, 1609, 1512, 1454, 1249, 1031, 832, 763, 699. Anal.Calcd for $C_{28}H_{27}N_3O_2$ (437.54): C, 76.86; H, 6.22; N, 9.60. Found: C, 76.80; H, 6.28; N, 9.55.

_N_-Benzyl-_N_-{(_E_)-3-phenyl-1-[5-(2-phenyl-1-ethynyl)-1,3,4-oxadiazol-2-yl]-2-propenyl}amine (5h)

Yellow Viscous oil (yield 88%),^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 2.30 (s, 1H, NH), 3.89 (s, 2H, CH_2), 4.81 (d, 1H, $^3J_{HH}$ =7.2 Hz, CH), 6.33 (dd, 1H, $^3J_{HH}$ =7.2 Hz, $^3J_{HH}$ =16.0 Hz, =CH), 6.71 (d, 1H, $^3J_{HH}$ =16 Hz, =CH), 6.83-7.63 (m, 15H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C (ppm) 51.15 (CH_2), 55.95 (CH), 125.00, 126.74, 127.42, 128.32, 128.41, 128.61, 128.70, 130.70, 132.35, 134.43 (17CH), 74.25, 92.50, 120.00, 135.69, 138.83 (5C), 166.95 (2C=N). IR (Neat) (υ_{max}, cm^{-1}): 3300, 3058, 2214, 1667, 1602, 1538, 1494, 1177, 722, 695. Anal.Calcd for $C_{26}H_{21}N_3O$ (391.46): C, 79.77; H, 5.41; N, 10.73. Found: C, 79.70; H, 5.47; N, 10.64.

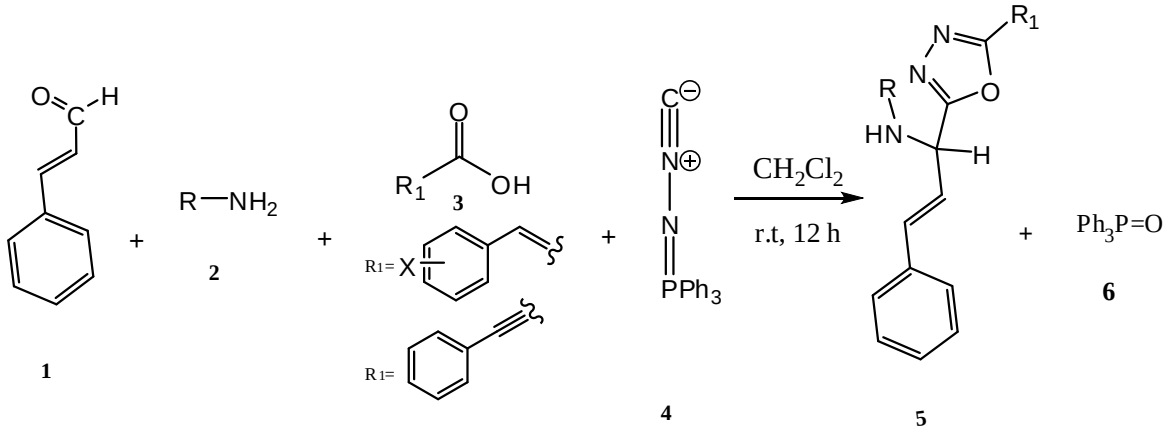
_N_-(4-Methylbenzyl)-_N_-{(_E_)-3-phenyl-1-[5-(2-phenyl-1-ethynyl)-1,3,4-oxadiazol-2-yl]-2-propenyl}amine (5i)

Yellow Viscous oil (yield 81%), ^{1}H NMR ($CDCl_3$, 250 MHz): δ_H (ppm) 1.65 (s, 1H, NH), 2.34 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 4.80 (d, 1H, $^3J_{HH}$ =7.2 Hz, CH), 6.33 (dd, 1H, $^3J_{HH}$ =7.2 Hz, $^3J_{HH}$ =15.5 Hz, =CH), 6.70 (d, 1H, $^3J_{HH}$ =15.5 Hz, =CH), 7.14-7.63 (m, 14H, CH_{arom}). IR (Neat) (υ_{max}, cm^{-1}): 3422, 3026, 2952, 2229, 1650, 1603, 1534, 1452, 1028, 812, 750, 699. Anal.Calcd for $C_{27}H_{23}N_3O$ (405.49): C, 79.97; H, 5.72; N, 10.36. Found: C, 79.90; H, 5.78; N, 10.41.

Results and discussion

The imine intermediate generated by the condensation reaction of cinnamaldehyde **1** with primary amines **2** is trapped by **4** and carboxylic acids 3, and leads to the formation

of 1,3,4-oxadiazole derivatives **5** and triphenylphosphine oxide **6** (Scheme 1). The reaction proceeds smoothly and cleanly under mild and neutral conditions (without addition of any acid or base) and no side reactions were observed.



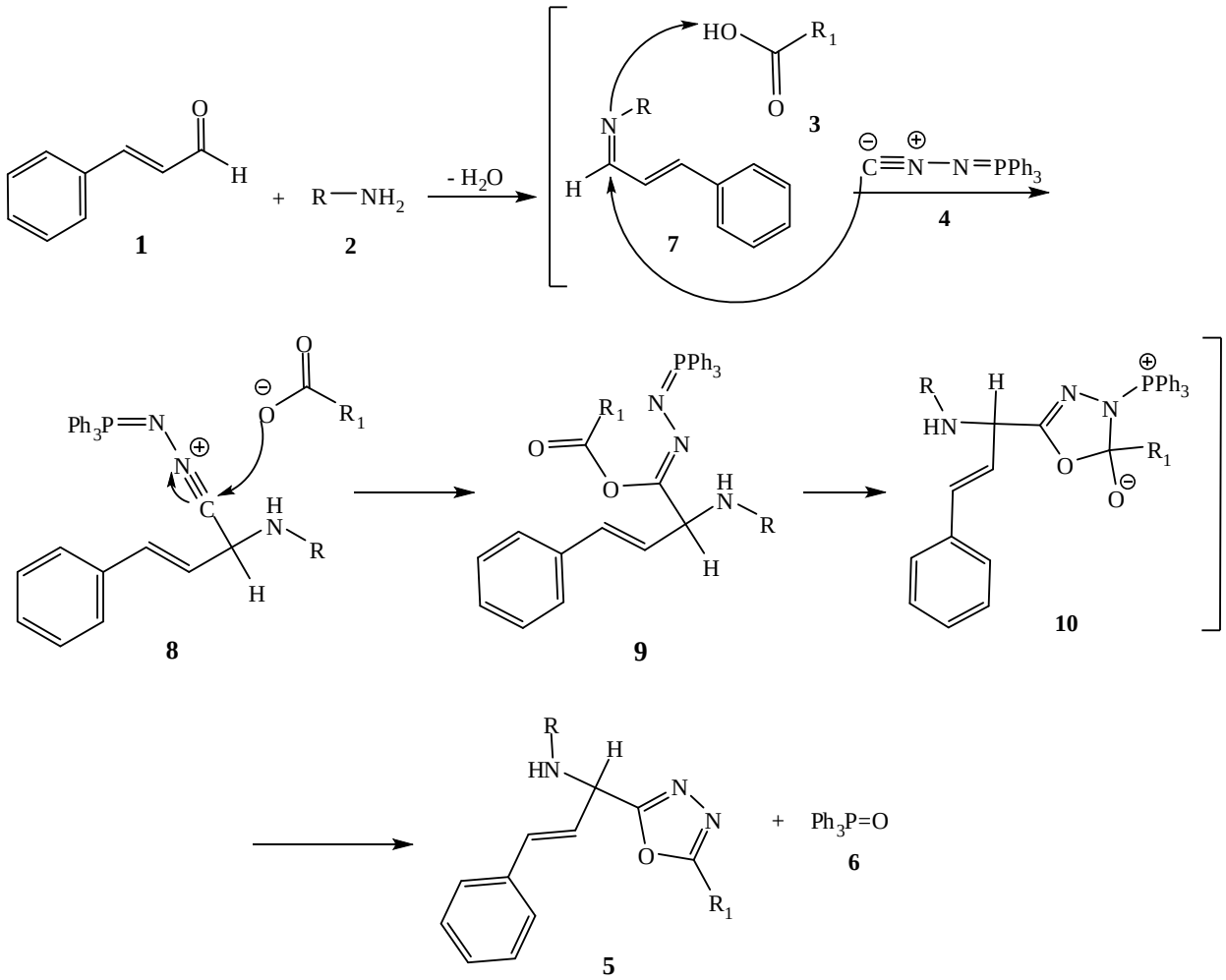
5a: R= 4-methylbenzyl, R_1= 4-chlorophenyl-1-ethenyl; **5b**: R= benzyl, R_1= 4-chlorophenyl-1-ethenyl; **5c**: R= benzyl, R_1= phenyl-1-ethenyl; **5d**: R= benzyl, R_1= 1-methyl-2-phenyl-1-ethenyl; **5e**: R= benzyl, R_1= 4-fluorophenyl-1-ethenyl; **5f**: R= 4-methoxybenzyl, R_1= 4-chlorophenyl-1-ethenyl; **5g**: R= 4-methoxybenzyl, R_1= 1-methyl-2-phenyl-1-ethenyl; **5h**; R= benzyl, R_1= phenylethynyl; **5i**: R= 4-methylbenzyl, R_1= phenylethynyl

Scheme 1. Four-component synthesis of 1,3,4-oxadiazoles 5

The structures of the products were deduced from their IR, ^{1}H NMR, ^{13}C NMR spectra, and mass spectrometry. For example, The ^{1}H NMR spectrum of **5a** consists of singlet for the methyl group (δ = 2.36 ppm), a singlet for the NH proton (δ = 2.38 ppm, exchangeable by D_2O), an AB pattern for the CH_2Ph group (δ = 3.89 ppm, $^2J_{HH}$ = 13.2 Hz), a doublet for the CH proton (δ = 4.84 ppm, $^3J_{HH}$ = 7.6 Hz), a doublet of doublet for the HC= CH protons (δ = 6.37 ppm, $^3J_{HH}$ = 7.6 Hz, and $^3J_{HH}$ = 15.6 Hz), two doublets for the HC= CH protons (δ = 6.74 ppm, $^3J_{HH}$ = 15.6 Hz, and 6.99 ppm, $^3J_{HH}$ = 16.4 Hz), and multiplet for the aromatic protons and =CH protons(δ = 7.07-7.55 ppm). The^{1}H decoupled ^{13}C NMR spectrum of **5a** shows 21 distinct resonances, partial assignment of these resonances is given in the experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **5b–i** are similar to those of **5a**, except for the vinilic, acetylenic and aromatic moieties, which exhibit characteristic signals with appropriate chemical shifts.

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 cinnamaldehyde **1** with the primary amines **2**. The next step may involve nucleophilic addition of the (*N*-isocyanimino)triphenylphosphorane **4** to the imine intermediate **7**, which is facilitated by its protonation with the carboxylic acid **3**, leading to nitrilium intermediate **8**. This intermediate may be attacked by the conjugate base of the carboxylic acid to form the 1:1:1 adduct **9**. The intermediate **9** then undergoes intramolecular *aza*-Wittig reaction [17-20] of iminophosphorane moiety with the ester carbonyl group to afford the isolated sterically congested 1,3,4-oxadiazole derivatives **5** by removal of triphenylphosphine oxide **6** from intermediate **10**.



Scheme 2. Proposed mechanism for the formation of 1,3,4-oxadiazoles 5

Conclusion

In summary, We believe that the reported method offers a mild, simple, and efficient route for the preparation of fully substituted 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.

Acknowledgments

This research was supported by the Iran National Science Foundation.

References

[1] J. Zhu, H. Bienaymé, Eds. Wiley. Weinheim, **2005**.

[2] A. Domling, *Chem. Rev*., **2006**, *106*, 17–89.

[3] I. Yavari, A. Mirzaei, Z. Hossaini, S. Souri, *Mol Divers*., **2010**, *14*, 343–347.

[4] A. Ramazani, F. Zeinali Nasrabadi, Z. Karimi, M. Rouhani, *Bull. Korean Chem. Soc*., **2011**, *32*, 2700-2704

[5] I. Ugi, B. Werner, A. Dömling, Molecules, **2003**, *8*, 53-66.

[6] I. Yavari, Z. Hossaini, M. Sabbaghan, *Mol Divers*., **2006**, *10*, 479-482.

[7] F. Zeinali Nasrabadi, A. Ramazani, Y. Ahmadi, *Mol Divers*., **2011**, *15*, 791–798.

[8] B.S. Holla, R.Gonsalves, S. Shenoy, *Eur. J. Med . Chem*., **2000**, *35*, 267-271.

[9] I. R. Baxendale, S. V. Ley, M. Martinelli, *Tetrahedron*., **2005**, *61*, 5323-5349.

[10] W.A. El-Sayed, F.A. El-Essawy, O.M. Ali, B.S. Nasr, M.M. Abdalla, A.H. Abdel-Rahman, *Monatsh. Chem*., **2010**, *141*, 1021-1028.

[11] Y.Wang, D.R. Sauer, S.W. Djuric, *Tetrahedron Lett*., **2006**, *47*, 105-108.

[12] F. Palacios, D. Aparicio, G. Rubiales, C. Alonso, JM. de los Santos, *Curr. Org. Chem*., **2009**, *13*, 810-828.

[13] H. Stolzenberg, B. Weinberger, WP. Fehlhammer, FG. Pühlhofer, R. Weiss, *Eur. J. Inorg. Chem*., **2005**, *21*, 4263-4271.

[14] (a) A. Ramazani, A. Bodaghi, *Tetrahedron Lett*., **2000**, *41*, 567-568; (b) P. Pakravan, A. Ramazani, N. Noshiranzadeh, A. Sedrpoushan, *Phosphorus, Sulfur, Silicon Relat. Elem*., **2007**, *182*, 545-549; (c) A. Ramazani, N. Shajari, F. Gouranlou, *Phosphorus, Sulfur, Silicon Relat. Elem*., **2001**, *174*, 223-227.

[15] (a) A. Ramazani, M. Rahimifard, A. Souldozi, *Phosphorus, Sulfur, Silicon Relat. Elem*., **2007**, *182*, 1-5; (b) A.Ramazani, M.. Rahimifard, N. Noshiranzadeh, A.Souldozi, *Phosphorus, Sulfur, Silicon Relat. Elem*., **2007**, *182*, 413-417.

[16] (a) A. Ramazani, E. Ahmadi, A. R. Kazemizadeh, L. Dolatyari, N. Noshiranzadeh, I.Eskandari, A. Souldozi,

Phosphorus, Sulphur, Silicon Relat. Elem., **2005**, *180*, 2419-2422; (b) A. Ramazani, I. Amini, A. Massoudi, *Phosphorus, Sulphur, Silicon Relat. Elem*., **2006**, *181*, 2225-2229.

[17] (a) A. Ramazani, A. Tofangchi Mahyari, M. Rouhani, A. Rezaei, *Tetrahedron Lett*., **2009** *50*, 5625–5627; (b) A. Ramazani, A. Rezaei, A. Tofangchi Mahyari, M. Rouhani, M. Khoobi, *Helv. Chim. Acta*., **2010**, *93*, *2033*-2036; (c) A. Ramazani, Y. Ahmadi, R. Tarasi, *Heteroatom. Chem*., **2011**, *22*, 79-84.

[18] (a) A. Souldozi, A. Ramazani, N. Bouslimani, R. Welter, *Tetrahedron Lett*., **2007**, *48*, 2617–2620; (b) A. Souldozi, A. Ramazani, *Tetrahedron Lett*., **2007**, *48*, 1549–1551; (c) A. Souldozi, A. Ramazani, *Phosphorus, Sulfur, Silicon Relat. Elem*., **2009**, *184*, 3191-3198.

[19] (a) A. Souldozi, A. Ramazani, *Phosphorus, Sulfur, Silicon Relat. Elem*., **2009**, *184*, 2344-2350; (b) A. Souldozi, A. Ramazani, *Arkivoc*., **2008**, *xvi*, 235-242; (c) A. Souldozi, K. Ślepokura, T. Lis, A. Ramazani, Z. Naturforsch, **2007**, *62b*, 835–840

[20] (a) A. Ramazani, A. Rezaei, *Org. Lett*., **2010**, *12*, 2852-2855; (b) A. Ramazani, Y. Ahmadi, M. Rouhani, N. Shajari, A. Souldozi, *Heteroatom Chem*., **2010**, *21*, 368-372.