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One-pot synthesis of 2-aryl-1,3,4-oxadiazole derivatives as potential antibacterial agents

Fatemeh Karimi[1], Ali Souldozi*[2] and Nima Hosseini Jazani[3]

[1]Department of Biology, Ahar Branch, Islamic Azad University, Ahar, Iran
[2]Department of Chemistry, Urmia Branch, Islamic Azad University, Urmia, Iran
[3]Department of Microbiology, Faculty of medicine, Urmia University of Medical Sciences, Urmia, Iran

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ABSTRACT

The reaction of carboxylic acid derivatives (benzoic acid, 3-(tolic acid, 4-tolic acid, mefenamic acid, anthranic acid) with (N-isocyanimino)triphenylphosphorane proceeds smoothly at room temperature to afford 2-aryl-1,3,4-oxadiazoles via an intramolecular aza-Wittig reaction in excellent yields under neutral conditions. The structures of the products were deduced from their IR, ^{1}HNMR, and ^{13}CNMR spectra and mass spectrometry. All the compounds have been screened for antibacterial activity against Escherichia coli ATCC 2921,Pseudomonas aeruginosa ATCC 27853, Staphylococcus aureusATCC 25923, Listeria monocytogenes ATCC 23074 and antimycobacterial activity against Mycobacterium smegmatis PTCC 1307by the broth dilution and well agar diffusion methods. The results revealed that compounds 5a and 5b have antibacterial activity against E.coli and compounds 5e and 5d showed anti-mycobacterial activity.

Keywords: one-pot synthesis, 1,3,4-oxadiazol, antimicrobial, antimycobacterial

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INTRODUCTION

Infectious diseases are responsible for great number of deaths in the world population. Today widespread excessive use of antibacterial agents to prevent infectious diseases leads to development of more resistant microorganisms to commonly used antibiotics [1].Thus, the infections caused by these microorganisms pose a severe challenge to the medical community and need for an effective therapy has led to a search for novel antimicrobial agents. For this reason, the present work is aimed toward developing molecules with potent antimicrobial activity to tackle this problem.

Several studies have shown that 1,3,4-oxadiazoles have wide spectrum of biological effects ranging from anti-inflammatory [3], anticonvulsant [4], antifungal [5], antibacterial [6-8], anticancer [9], anthelmintic [10] and analgesic [11]. A significant number of drugs which are commonly available have oxadiazole ring as a structural building block (for example Raltegravir, Butalamine, Fasiplon). Various methods have been reported for the synthesis of 1,3,4-oxadiazoles. These methods essentially have multi stages [12-17]. The most common method uses the cyclization of diacylhydrazides with a variety of reagents, such as thionylchloride, phosphorous oxychloride, or sulfuric acid, usually under unfavorable reaction conditions [18-22]. In the present study an unfamiliar two-component reaction, which, starting from easily accessible benzoic acid derivatives affords 2-aryl-1,3,4-oxadiazoles in a one-pot reaction with (*N*-isocyanimino)triphenylphosphorane is reported. All the synthesized compounds were tested in respect of their antibacterial activities against a number of gram positive, gram negative and acid-fast bacteria.

EXPERIMENTAL SECTION

Chemistry

^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR measurements were recorded on a Bruker 250 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. IR spectra were measured on a Shimadzu IR-460 spectrometer. Elemental analyses for C and H 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 20 eV. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. (*N*-Isocyanimino) triphenylphosphorane **2** was prepared based on a reported procedure [23, 24]. Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Flash chromatography columns were prepared from Merck silica gel powder. The structures of the products were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values.

General Procedure for the Preparation of products (5a-e)

To a magnetically stirred solution of (*N*-isocyanimino)triphenylphosphorane (**2**) (0.302 g, 1 mmol) in CH_2Cl_2 (8 ml) was added drop-wise a solution of **1**(1 mmol) in CH_2Cl_2 (7 ml) over 15 min. The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel; petroleum ether–ethyl acetate (8:1). The solvent was removed under reduced pressure and the products (**5a–e**) were obtained.

2-Phenyl-1,3,4-oxadiazole (5a)

White crystals; mp: 143.6 ^{o}C; Yield: 91%. IR (KBr)(ν_{max}, cm^{-1}): 3008, 1692, 1661, 1530, 723. ^{1}HNMR ($CDCl_3$, 250 MHz): δ_H 8.42 (s, 1H, oxadiazole); 8.11-8.05 (m, 2H, arom); 7.59-7.48 (m, 3H, arom). ^{13}CNMR ($CDCl_3$, 62.5 MHz): δ_C 164.79 (1C, oxadiazole); 152.67 (1CH, oxadiazole); 132.03, 129.13, and 127.10 (5CH, arom), 123.42 (1C, arom). Elemental Anal.Calcd. (%) for $C_8H_6N_2O$ (146): C, 65.75; H, 4.14; N, 19.17. Found: C, 65.70; H, 4.39; N, 19.11. MS (EI) (m/z): 51 (27), 77 (80), 105(100), 146 (2).

2-p-Tolyl-1,3,4-oxadiazole (5b)

White crystals; mp: 86.9 ^{o}C; Yield: 93%. IR (KBr) (ν_{max}, cm^{-1}): 3123, 2915, 1615, 1500, 1100, 954, 831, 738. ^{1}HNMR ($CDCl_3$, 250 MHz): δ_H 8.44 (s, 1H, oxadiazole); 7.99-7.83 (m, 2H, arom); 7.34-7.18 (m, 2H, arom); 2.43 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$, 62.5 MHz): δ_C 164.89 (1C, oxadiazole); 152.37 (1CH, oxadiazole); 142.58 and 120.70 (2C, arom); 129.81 and 127.03(4CH, arom); 21.65 (1C, CH_3). Elemental Anal. Calcd. (%) for $C_9H_8N_2O$ (160): C, 67.49; H, 5.03; N, 17.49. Found:C, 67.55; H, 5.09; N, 17.43. MS (EI) (m/z): 41 (40), 43 (83), 51 (74), 65 (52), 77 (84), 91 (55), 104 (35), 119 (92), 160 (100).

2-m-Tolyl-1,3,4-oxadiazole (5c)

White crystals; mp: 64.4 ^{o}C; Yield: 92%. IR (KBr) (ν_{max}, cm^{-1}): 3108, 2985, 2408, 2277, 1554, 1500, 1115, 731. ^{1}HNMR ($CDCl_3$, 250 MHz): δ_H 8.46 (s, 1H, oxadiazole); 7.90-7.80 (m, 2H, arom); 7.43-7.31 (m, 2H, arom); 2.43 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$, 62.5 MHz): δ_C 164.90 (1C, oxadiazole); 152.56 (1CH, oxadiazole); 132.80, 129.01, 127.61, 124.21 (4CH, arom); 139.02, 123.33 (2C, arom); 21.32 (1C, CH_3). Elemental Anal.Calcd. (%) for $C_9H_8N_2O$ (160): C, 67.49; H, 5.03; N, 17.49. Found:C, 67.42; H, 5.11; N, 17.43. MS (EI) (m/z): : 41 (17), 51 (24), 57 (26), 77 (35), 91 (31), 104 (22), 119 (79), 149 (67), 160 (100).

(2,3-Dimethyl-phenyl)-(2-[1,3,4]oxadiazol-2-yl-phenyl)-amine(5d)

Light yellow crystals. Yield: 89%, m. p.: 118.1-119.5 ^{o}C. IR (KBr)(ν max, cm^{-1}): 3316, 3138, 2930, 1615, 1584, 1507, 1453, 1323, 1276, 746 cm^{-1}. ^{1}HNMR ($CDCl_3$, 250 MHz): δ_H 2.23 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 6.77-6.88 (m, 2H, arom), 7.05-7.31 (m, 4H, arom), 7.87 (d, $^3J_{HH}$= 7.8 Hz, 1H, Ar-H), 8.45 (s, 1H, oxadiazole), 9.11 (s, 1H, NH). ^{13}CNMR ($CDCl_3$, 62.5 MHz): δ_C 113.6, 116.8, 123.4, 126.0, 127.1, 128.3, 132.8 (7CH, Ar-CH), 105.8, 138.3, 138.6, 146.2 (4C, Ar-C), 151.0 (1CH, oxadiazole), 164.7 (1C, oxadiazole). Elemental Anal. Calcd. (%) for $C_{16}H_{15}N_3O$ (265): C, 72.43; H, 5.70; N, 15.84. Found (%): C, 71.87; H, 5.63; N, 15.91. MS m/z: 41 (48), 43 (81), 57 (42), 77 (67), 91 (30), 149 (33), 167 (21), 180 (45), 194 (100), 208 (62), 223 (65), 241 (58), 265 (59), 266 (15).

2-(1,3,4-oxadiazol-2-yl)aniline(5e)

Light yellow crystals; Yield: 140 mg (86%); mp: 145.3-145.4 ^{o}C. IR (KBr)(ν_{max}, cm^{-1}): 3431, 3339, 3039, 2939, 2931, 2931, 1623, 1269, 1108, 754 cm^{-1}. ^{1}HNMR ($CDCl_3$, 250 MHz): δ_H 5.69 (br., s, 2H, NH_2), 6.73 (s, 1H, arom.),6.79 (t, 1H, $^3J_{HH}$ = 7.5 Hz, arom.), 7.75 (t, 1H, $^3J_{HH}$ = 7.8 Hz, arom.); 7.76 (d, 1 H,$^3J_{HH}$= 6.0 Hz, arom.); 8.41 (s, 1 H, oxadiazole).^{13}CNMR ($CDCl_3$, 62.5 MHz): δ_C116.28, 116.91, 127.99 and 132.79 (4 CH, arom.); 105.38 and 147.01 (2C, arom.); 150.91 (1CH, oxadiazole); 164.62 (1C, oxadiazole). Elemental Anal. Calcd. (%) for $C_8H_7N_3O$ (161): Calcd (%): C 59.62, H 4.38, N 26.07; Found (%): C 59.57, H 4.34, N 26.14. MS: *m/z* 41 (21), 51 (32), 65 (28), 77 (35), 92 (26), 105 (21), 120 (51), 161 (100).

Antibacterial evaluation

Agar Diffusion Method-Individual compounds Solutions

The antibacterial effects of synthesized compounds was determined with the well diffusion method as described by Parekh et al(2005) against a number of gram positive and gram negative bacteria, including *E.coli*ATCC 2921, *P.aeruginosa*ATCC 27853(both are gram-negative bacteria), *L.monocytogenes*ATCC 23074 and *S.aureus*ATCC 25923(both are gram-positive bacteria) with slighter formations [2]. In short, each compound was dissolved in DMSO and a solution with1mg/ml concentration was prepared. 200 ml of Muller Hinton Agar was melted over a boiling water bath then was stabilized at 45˚C and aseptically seeded with 100 µl inoculum, containing 0.5×10^6 cells/ml of bacteria, transferred into a sterile Petri dish. Wells were made in agar using a sterile glass tube and 50µl of compounds was transferred to each well. 50 µl of DMSO was inoculated into another well as a negative control. The antibacterial activity of compounds was determined by measuring the zones around each well against defined bacteria after incubation for 24h. Ceftizoxime and Ciprofloxacin used with the same method as standard antibacterial agents.

Broth dilution method

In the next step antimicrobial activity of compounds was evaluated by broth dilution method. The aim of this method is determining the lowest concentration of an antimicrobial agent that, under defined conditions, inhibits the visible growth of the tested organism which is considered by the lack of turbidity in a broth medium. Minimum Inhibitory Concentration (MIC) values are used in order to determining the susceptibility of the organism to antibiotics and new antibacterial agents. In this study sterile glass test tubes containing Muller Hinton Broth was used.10 µL of inoculum contained 1.5×10^{-6}C.F.U/ml of tested microorganism was added to each test tube. The concentration range of tested compounds was between 1000-3.5 µg/ml. Minimum Bactericidal Concentration (MBC) values were determined by sub culturing of the tested tubes on agar media that do not contain the antibacterial agent. The MBC is determined by detecting the lowest concentration of compounds that reduces the viability of the bacterial inoculums by ≥99.9%. The half maximal inhibitory concentration (IC_{50}) obtained by calculating the percentage of inhibition as it was described elsewhere [26] Ceftizixime and ciprofloxacin (Merck Aldrich) was used as standard antimicrobial agents.

Determination of IC50

According to the FDA, IC50 represents the concentration of a drug that is required for 50% inhibition *In Vitro*. It is obtained from the %inhibition and the concentration of used compound. IC50 was calculated by using the formula:

$$\frac{\text{Concentration of compound}}{\text{Inhibition \%}} \times 50$$

IC50 value were calculated by making use of MBC value [26].

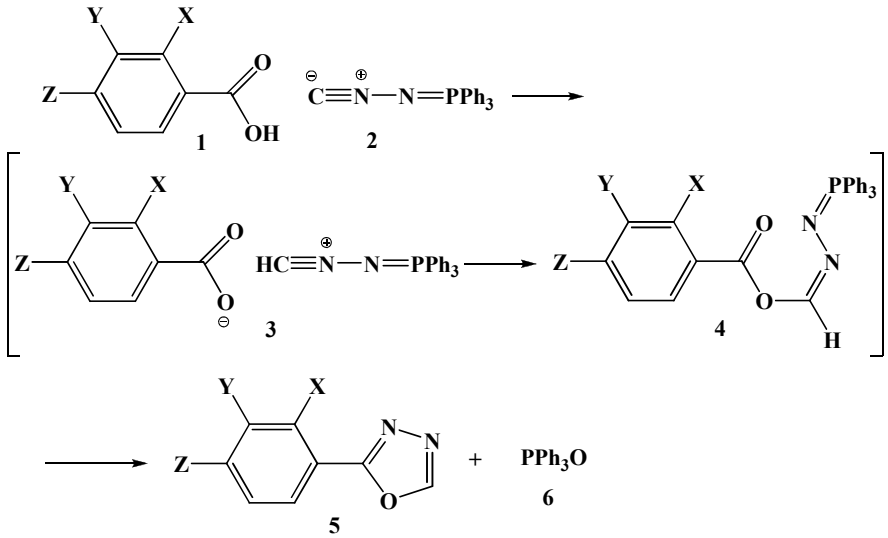
Antimycobacterial activity

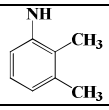
All products were evaluated *in vitro* for their antimycobacterial activity against *M. smegmatis* by the agar diffusion method. 25 ml *Middlebrook 7H10 Agar* was melted over a boiling water bath then was stabilized at 45˚C and aseptically seeded with 100 µl inoculum, containing 2.0×10^6cells/ml of *M. smegmatis PTCC 1307* and transferred into a sterile petri dish [29].Wells were made in agar using a sterile glass tube .100µl of 1mg/ml concentration of each compound in DMSO was transferred to each well. DMSO was used as negative control. The zones of inhibition (ZOI) were detected by measuring the diameter of clear area around the edges of the wells after 72hr of incubation in 37 ºC [30].

RESULTS AND DISCUSSION

Chemistry

The benzoic acid derivative (1) and (*N*-isocyanimino)triphenylphosphorane (2) inCH_2Cl_2 react together in a 1:1 ratio at room temperature to produce 2-aryl-1,3,4-oxadiazoles (5) and triphenylphosphine oxide (6) (Scheme 1). The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed. The mechanism of the reaction between the benzoic acid derivative (1) and (*N*-isocyanimino)triphenylphosphorane(2) has not been established experimentally. However, a possible explanation is proposed in Scheme 1. On the basis of the well-established chemistry of isocyanides [25], it is reasonable to assume that the protonation of 2 by carboxylic acid 1 followed by quenching of the cationic center by the conjugate base of the carboxylic acid can generate iminophosphorane 4.Intramolecularaza-Wittigreaction of iminophosphorane 4 would lead to the formation of 2-aryl-1,3,4-oxadiazoles 5 and triphenylphosphine (6) (Scheme 1).



5	X	Y	Z
a	H	H	H
b	H	CH_3	H
c	H	H	CH_3
d		H	H
e	NH_2	H	H

Scheme 1. Proposed Mechanism for the formation of 2-aryl-1,3,4-Oxadiazole Derivatives

Determination of the in Vitro Antimicrobial Activity

As shown in Table 1, most of the compounds **5a**–**e** at the concentration of 1mg/ml exhibited notable antibacterial activity against tested gram positive and gram negative bacteria except *L. monocytogenes*. The inhibition zones ranged from 9±0.7mm to 15±1mm (Table 1). Compound 5a showed the best activity against *E.coli* (15±1), however no activity was seen against *L.monocytogenes.* However there were significant differences in mean zones of inhibition between positive controls and synthesized compounds. No zone of inhibition was seen around the well containing DMSO (Negative control).

Table 2 shows the MIC and MBC values of the compounds against all the tested microorganisms. As shown in table 2 for all compounds MBC values are remarkably higher than MICs.

Table 1: *In vitro* antibacterial activity of 2-Substituted 1,3,4-Oxadiazole derivatives (inhibition zone, mm)by the well diffusion method

Comp. code	*E.coli ATCC 2921*	Microorganisms *P. aeruginosa ATCCT 27853*	*S. aureus ATCC 25923*	*L.monocytogenes* ATCC 23074
5a	14±1.00	10±0.00	10±1.52	NA
5b	13±1.52	11±0.57	9±1.15	NA
5c	12±0.57	12±0.57	10±0.00	NA
5d	11±1.52	NA	NA	NA
5e	10±0.00	11±1.00	12±1.00	NA
ceftizoxime	17±0.57	20±1.52	35±0.57	33±0.00
ciprofloxacin	44±0.00	42±1.15	45±0.57	45±1.00

These results are average results of three experiments; the compounds were used at the concentration of 1 mg/ml and the inhibition zones are stated in mm; NA = not active; diameter of inhibition zone ≤ 5 mm.

The results of determining MIC and MBC values revealed that all the synthesized compounds were fairly active against all tested bacteria. Compounds 5a and 5b showed maximum activity against *E. coli*, but the concentration of the compounds for exerting antibacterial activity are notably more in compare with positive controls (Ceftizoxime and Ciprofloxacin).

Table 2: *In vitro* antibacterial activity of 2-Substituted 1,3,4-Oxadiazole derivatives by broth dilution method(µg/mL)

Compounds code	*E.coli ATCC 2921*	Microorganism MIC-(MBC) *P.aeruginosa ATCCT 27853*	*S. aureus ATCC 25923*	*L.monocytogenes* ATCC 23074
5a	62.5(125)	250(1000)	1000(1000)	500(1000)
5b	62.5(125)	250(1000)	500(1000)	500(1000)
5c	250(500)	250(1000)	250(500)	250(500)
5d	250(500)	250(1000)	500(1000)	1000(1000)
5e	250(500)	250(1000)	250(500)	500(1000)
ceftizoxime	10(10)	10(10)	0.15(0.31)	0.07(0.15)
ciprofloxacin	0.07(0.15)	10(10)	0.039(0.07)	0.039(0.07)

MIC = minimum inhibitory concentration, MBC= minimum bactericidal concentration. Each experiment was performed in triplicate.

IC50 values were depicted in figure1. It is clearly indicated that the compound 5a yielded the best results when compared to other synthesized compounds.

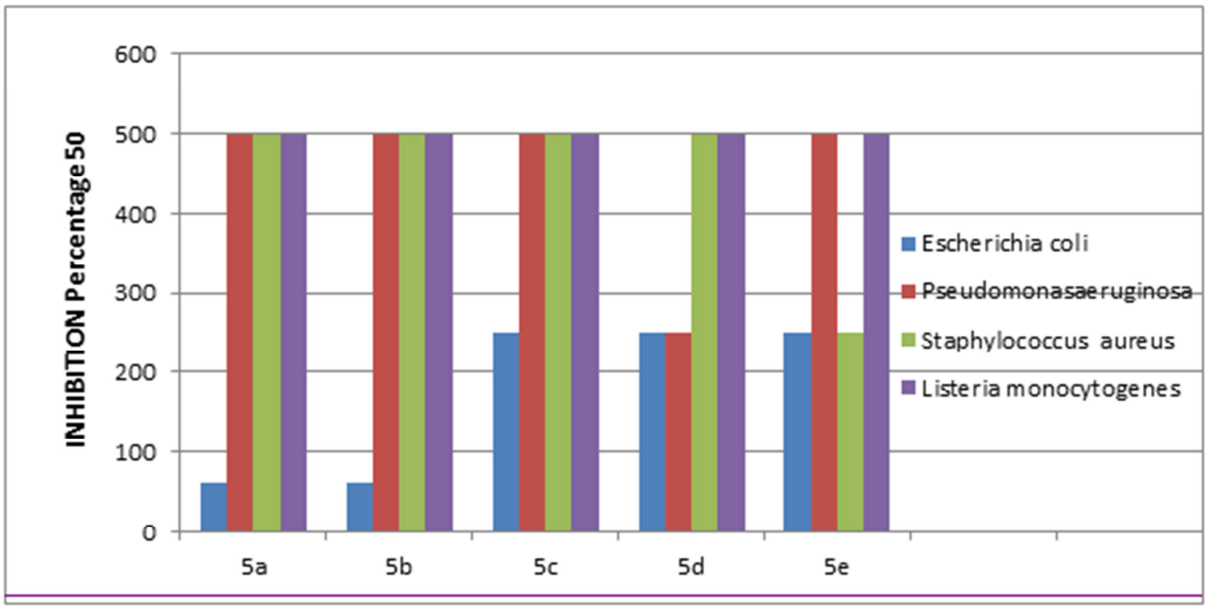


Figure 1. Microbicidal nature of compounds with reference to % inhibition

Antimycobacterial activity

In vitro antimycobacterial activity of 2-Substituted 1,3,4-Oxadiazole derivatives are shown in Table 3.

Table3: *In vitro* antimycobacterial activity of 2-Substituted 1,3,4-Oxadiazole derivatives (inhibition zone, mm)

No.	Inhibition zone(mm)
5a	12
5b	13
5c	12
5d	16
5e	15
Ceftizoxime	15
Ciprofloxacin	16
DMSO	0

D − d ≥ 25 mm: Very high activity; D − d ≥ 20 mm: High activity; D − d ≥ 15 mm: Average activity; D − d ≤ 15 mm: Low activity [31].

Among the ,2-Substituted 1,3,4-Oxadiazole derivatives, (2,3-Dimethyl-phenyl)-(2-[1,3,4]oxadiazol-2-yl-phenyl)-amine analog 5d and 2-(1,3,4-oxadiazol-2-yl)aniline analog 5e showed significant antimycobacterial activity. the presence of an aniline group at the 5nd position of oxadiazol in analog 5e and high Lipophilicity of analog 5d may make them more capable of penetrating waxy membranes, so improve their permeation into mycobacterial cell wall[27].Correlation between lipophilicity and anti TB effects has been described before[28].

CONCLUSION

The present study has showed that the effect of 1,3,4-Oxadiazole derivatives in respect of their *in vitro* antibacterial and antimycobacterial activities is influenced by the choice of the substituentat in the C-5 positions. The present of an aniline group and (2,3-Dimethyl-phenyl)-amine group in theC-5 position markedly improved *in vivo* antimycobacterial activity. Furthermore the easy workup, high yield and short reaction times make it a useful addition to modern pharmaceutical synthetics.

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