Introduction

Oxadiazole is a class of five membered heterocyclic aromatic compounds with the molecular formula C₂H₂N₂O. It is composed of two atoms of carbon, two atoms of nitrogen and one atom of oxygen. They were first discovered in 1884 by Tiemann and Krüger. It has four isomers 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole (Figure 1). 1,2,3-oxadiazole isomer is unstable and ring-opens to form the diazoketone tautomer but the other isomers are stable and known [1].

Due to the biological significance of 1,3,4-oxadiazoles this work is concerned with the synthesis and reactions of new 5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-amine 1. The parent oxadiazole 1 was obtained from reaction of 4-chlorophenylacetic acid with semicarbazide in the presence of phosphorus oxychloride followed by addition of potassium hydroxide. Acylation of amino oxadiazoles 1 with acid chlorides such as acetyl chloride, benzoyl chloride, 3-nitrobenzoyl chloride, 4-methoxybenzoyl chloride, 4-tert-butylbenzoyl chloride and chloroacetyl chloride in the presence of triethylamine yielded the acylated compounds 2-7. Reaction of phenyl isocyanate and 3-chlorophenyl isocyanate with oxadiazole 1 afforded the urea derivatives 8 and 9. Cyclization of acetamide 7 by reaction with ammonium thiocyanate gave thiazolidinone 10. Coupling of chloacetamide 7 with mercapto derivatives in the presence of diisopropylethylamine gave oxadiazole derivatives 11-13. New compounds were obtained in a good yield and elucidation was done using mass spectrometry, ¹H-NMR and ¹³C-NMR.

Keywords Phenylacetic acid, 1,3,4-oxadiazoles, Acid chloride, Thiazolidinone, Coupling

Oxadiazole derivatives obtained by hydroxylation, alkoxylation and alkylation or amination of the parent oxadiazole. They are representing an important synthetic heterocyclic compounds and substitutions in various positions on oxadiazole ring influence its properties.

Oxadiazole nucleus appear in a variety of pharmaceutical drugs such as Raltegravir and Pleconaril which used as antivirals, Butalamine is a vasodilator, Fasiplon which is a nonbenzodiazepine anxiolytic drug and Oxolamine whose cough suppressant [2-5] (Figure 2).

Fig.1. Isomers of oxadiazole
Moreover, the widespread application of oxadiazoles in medicinal chemistry confirmed that this moiety is an important bioactive class of heterocycles [6]. They have been found to exhibit diverse biological activities such as antimicrobial, antioxidant [7], herbicides [8], antimalarials [9], antihypertensives [10], anti-inflammatories [12], and antibacterials [13]. There are different methods for preparation of oxadiazole derivatives that have been reported in the literature [14-15]. 1,3,4-Oxadiazoles were synthesized by direct annulation of hydrazides with alkyl ketones [16]. Another new and efficient method is the oxidative cyclization of aroyl hydrazones catalyzed by Fe(III)/TEMPO. This reaction offered a broad scope and good functional-group tolerance [17].

In this paper, I have reported the synthesis of a thirteen new oxadiazole derivatives. Structures of new synthesized compounds were confirmed on the basis of mass spectroscopy, 1H-NMR and 13C-NMR.

**Results and Discussion**

4-Chlorophenylacetic acid was reacted with semicarbazide in the presence of phosphorus oxychloride followed by addition of potassium hydroxide till basicity to give 5-(4-chlorobenzyl)-1,3,4-oxadiazole-2-amine 1. Acylation of 1 was explored that it was done on the amino group. A number of acid chlorides was used which include; acetyl chloride, benzoyl chloride, 3-nitrobenzoyl chloride, 4-methoxy-benzoyl chloride, 4-tert-butylbenzyl chloride, and chloroaecetyl chloride to produce N-acylamino oxadiazole derivatives 2-7 (Scheme 1). Refluxing the oxadiazole 1 with phenyl isocyanate or 3-chloro-phenyl isocyanate afforded 1-(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl)-3-phenylurea 8 and 1-(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl)-3-(3-chlorophenyl)urea 9 respectively (Scheme 1).

Oxadiazole 7 was cyclized by reaction with ammonium thiocyanate to yield 2-(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl-imino) thiazolidin-4-one 10. Alkylation of the mercapto derivatives; thiophenol, 2-mercapto benzothiazole or 2-mercapto-4,5-dihydro-thiazole with the chloro-oxadiazole 7 resulted in S-alkylation to afford N-(5-(4-bromobenzyl)-1,3,4-oxadiazol-2-yl)-2-(phenylthio)acetamide 11, N-(5-(4-bromobenzyl)-1,3,4-oxadiazol-2-yl)-2-(benzo[d]thiazol-2-ylthio) acetamide 12 and 2-(4,5-dihydrothiazole-2-ylthio)-N-(5-(4-bromobenzyl)-1,3,4-oxadiazol-2-yl) acetamide 13 respectively (Scheme 2).

**Structure confirmation**

Structure of 5-(4-Chlorobenzyl)-1,3,4-oxadiazole-2-amine has been confirmed by 1H-NMR where 4-chlorophenyl ring revealed two doublets at 7.02 and 7.45 ppm for the four aromatic protons. Characteristic singlet of methylene group appeared at 4.12 ppm and the amino group was found as a singlet at 7.13 ppm. 13C-NMR of 1 revealed the two carbons of oxadiazole ring around 157.3 and 169.0 ppm. Six carbon of 4-chlorophenyl was appearing between 137.7 and 120.2 ppm. The methylene carbon appeared at 35.6 ppm.

1H-NMR of compounds 2-7 showed the NH signal around 11.50 ppm. 1H-NMR of 8 and 9 displayed the NH group at 7.13 ppm. 13C-NMR of 1 revealed the two carbons of oxadiazole ring around 157.3 and 169.0 ppm. Six carbon of 4-chlorophenyl was appearing between 137.7 and 120.2 ppm. The methylene carbon appeared at 35.6 ppm.
**Materials and Methodology**

**Chemicals and Instruments**

Standard chemicals of Sigma-Aldrich were obtained from chemical laboratory. The purity of the synthesized compounds was checked by TLC on glass coated plates in the laboratory with silica gel GF 254 type, 60 mesh, size 50-250. MEL-TEMP II melting point apparatus was used to measure the melting points of the crystals. Mass spectra were measured with a Thermo Scientific LTQ Linear Ion Trap. Nuclear magnetic resonance spectra (1H-NMR, 13C-NMR) were recorded (δ in ppm) on Bruker spectrometer (300 MHz), at room temperature (DMSO-d6 as solvent).

**Methodology**

**Synthesis of 5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-amine**

A mixture of 4-chlorophenylacetic acid (1.0 mmol) and semicarbazide (1.0 mmol) in 3.0 mL.

of phosphorus oxychloride were heated for 1 hr. After that, the reaction cooled to room temperature followed by addition of 3.0 mL of water carefully. The mixture was refluxed for 4 hours, filtered on hot and the solid was wash with warm water and the filtrate was basified with saturated potassium hydroxide. The precipitate was filtered off and recrystallized from ethanol.

5-(4-Chlorobenzyl)-1,3,4-oxadiazole-2-amine 1

Yield 70%; mp: 180-182°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 4.12 (s, 2H, -CH2-), 7.13 (s, 2H, -NH), 7.02 (d, 2H, J = 8.18 Hz), 7.45 (d, 2H, J = 8.079 Hz); 13C-NMR (DMSO-d6, δ ppm): (169.0, 157.3, 137.4, 132.1, 131.7, 120.2, 35.6); ESI-MS: 209 (100 %), 211 (31 %).

Acetylation reaction of oxadiazole 1 by acid chloride 2-7

A mixture of 5-(4-Chlorobenzyl)-1,3,4-oxadiazole-2-amine 1 (1.0 mmol) in methylene chloride (20.0 mL) containing (0.069 mL, 0.5 mmol) triethylamine was stirred for 15 minutes then 0.5 mmol of the appropriate acid chloride was added and the mixture was stirred at room temperature for 24 hr. Product was extracted by EtOAc and recrystallized by ethanol.

N-(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)acetamide 2

Yield 73%; mp: 260-262°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 2.13 (s, 3H, -CH3), 3.95 (s, 2H, -CH2-), 7.31 (d, J = 8.24 Hz, 2H), 7.91 (d, J = 8.202 Hz, 2H), 12.31 (s, 1H, -NH); 13C-NMR (DMSO-d6, δ ppm): (169.4, 165.8, 163.5, 132.4, 131.9, 129.7, 129.2, 32.4, 24.6); ESI-MS: 251 (100 %), 253 (33 %).

N-(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)benzamide 3

Yield 76%; mp: 274-275°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 4.34 (s, 2H, -CH2-), 7.12 (d, J = 8.199 Hz, 2H), 7.23 (d, J = 8.020 Hz, 2H), 8.01 (d, J = 8.3310 Hz, 2H), 7.52 (t, J = 2.53 Hz, 2H), 7.92 (t, H, -CH2-), 12.13 (s, 1H, -NH); 13C-NMR (DMSO-d6, δ ppm): (166.1, 165.6, 163.3, 137.7, 137.1, 133.2, 132.1, 131.6, 129.7, 129.2, 120.6, 34.8); ESI-MS: 313 (100 %), 315 (32 %).

N-(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)-3-nitrobenzamide 4

Yield 71%; mp: 281-283°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 4.12 (s, 2H, -CH2-), 7.01 (d, J = 8.24 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.77 (t, 1H), 8.12-8.51 (dd, 2H), 8.72 (s, 1H), 12.11 (s, 1H, -NH); 13C-NMR (DMSO-d6, δ ppm): (165.9, 162.8, 161.1, 147.9, 137.1, 135.6, 134.3, 132.2, 131.9, 130.1, 127.2, 123.8, 120.5, 542); ESI-MS: 358 (100 %), 360 (31 %).

N-(5-(4-Bromobenzyl)-1,3,4-oxadiazole-2-yl)-4-methoxybenzamide 5

Yield 68%; mp: 264-266°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 3.21 (s, 3H, -CH3), 4.14 (s, 2H, -CH2-), 7.06 (d, J = 8.61 Hz, 2H), 7.31 (d, J = 7.95 Hz, 2H), 7.53 (d, J = 8.13 Hz, 2H), 8.24 (d, J = 8.85 Hz, 2H), 12.02 (s, 1H, -NH); 13C-NMR (DMSO-d6, δ ppm) (167.1, 165.1, 163.6, 160.5, 137.2, 132.1, 131.7, 131.6, 122.8, 120.2, 113.9, 58.3, 34.2); ESI-MS: 343 (100 %), 345 (32 %).

N-(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)-4-tert-butylbenzamide 6

Yield 62%; mp: 281-283°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 1.31 (s, 9H, -CH3), 4.16 (s, 2H, -CH2-), 7.03 – 8.13 (m, 8H, ArH), 11.81 (s, 1H, -NH); 13C-NMR (DMSO-d6, δ ppm): (165.8, 161.2, 160.8, 157.1, 133.6, 132.4, 131.2, 129.1, 125.9, 125.1, 121.5, 35.6, 34.5, 31.7); ESI-MS: 369 (100 %), 371 (32 %).

N-(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)chloroacetamide 7

Yield 78%; mp: 221-223°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 4.45 (s, 2H, -CH2-), 4.26 (s, 2H, -CH2-), 7.15 (d, J = 8.31 Hz, 2H), 7.53 (d, J = 8.34 Hz, 2H), 12.12 (s, 1H, -NH); 13C-NMR (DMSO-d6, δ ppm): (166.6, 164.8, 160.2, 137.1, 131.7, 131.2, 120.3, 41.5, 34.2); ESI-MS: 285 (100 %), 287 (60 %).

4.2.3- Reaction of oxadiazole 1 with phenyl isocyanate 3-chlorophenyl isocyanate

5-(4-Chlorobenzyl)-1,3,4-oxadiazole-2-amine 1 (0.15 g, 0.5 mmol) was dissolved in ethanol 15.0 mL followed by adding of (0.5 mmol) phenyl isocyanate or 3-chlorophenyl isocyanate. The reaction mixture refluxed for 8 hrs. The precipitate was filtered off and recrystallized from ethanol.

1-(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)-3-phenylurea 8

Yield 67%; mp: 164-166°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 4.19 (s, 2H, -CH2-), 7.16 – 7.86 (8H Ar), 8.84 (s, 1H, -NH), 12.12 (s, H, -NH); 13C-NMR (DMSO-d6, δ ppm): (162.3, 160.2, 152.1, 132.9, 132.5, 131.2, 130.3, 128.3, 124.6, 123.1, 120.3, 35.2); ESI-MS: 328 (100 %), 330 (31 %).

1-(5-(4-Chlorobenzyl)-1,3,4-oxadiazol-2-yl)-3-(3-Chlorophenyl)urea 9

Yield 65%; mp: 182-183°C; 1H-NMR (300 MHz, DMSO-d6, δ ppm): 4.13 (s, 2H, -CH2-),

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7.31 – 7.82 (8H Ar), 9.10 (s, 1H, -NH), 11.83 (s, H, -NH); 13C-NMR (DMSO-d6, δ ppm): (166.1, 162.5, 154.2, 143.9, 137.1, 133.2, 132.4, 131.2, 130.6, 122.2, 121.3, 119.1, 118.2, 34.9); ESI-MS: 362 (100 %), 364 (31 %).

4.2.4- Synthesis of 2-(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl iminothiazolidin-4-one 6

A Mixture of N-(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl)-2-chloroacetamide 7 (1.0 mmol) and ammonium thiocyanate (2.1 mmol) in ethanol 40.0 mL was refluxed for 4 hrs. the reaction mixture was left overnight. The precipitate was filtered off, dried and recrystallized from ethanol.

2-(5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-yl iminothiazolidin-4-one 6

Yield 63%, mp: 263-265°C. 1H-NMR (300 MHz, DMSO-d6, δ ppm): 3.01 (t, 2H, -CH2), 4.13 (t, 2H, -CH2), 4.21 (s, 2H, -CH2), 7.16 (d, J= 8.33 Hz, 2H), 7.82 (d, J= 8.35 Hz, 2H), 12.01 (s, H, -NH); 13C-NMR (DMSO-d6, δ ppm): (170.7, 166.7, 165.6, 162.9, 132.8, 131.9, 130.7, 120.9, 69.3, 34.8, 30.6, 29.6). ESI-MS: 368 (100 %), 370 (39%).

Conclusion

In this article, new simple and efficient method for the synthesis of a series of new 5-(4-chlorobenzyl)-1,3,4-oxadiazol-2-amine derivatives in good yields and high purity was developed. The starting material was synthesized from 4-chlorophenylacetic acid which is available commercially. Cyclization of 7 was successfully done to give 10. Moreover, the chloro derivative 7 was used for the alkylation of 3 aromatic thiois to afford the S-alkylated products 11-13. Spectroscopic tools such as mass spectroscopy which confirming molecular weight of them. 1H-NMR spectroscopy elucidates number, position and type of protons. 13C-NMR spectroscopy was determining carbon atoms and number of hydrogens bonded with each carbon. Further studies are being conducted to acquire more information about biological activities such as antimicrobial, antioxidant or antifungals activity with study of quantitative structure-activity relationships (QSAR).

References


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