ORIGINAL RESEARCH ARTICLE

A CONVENIENT SYNTHESIS OF 3-ARYL-5-HYDROXYALKYL-1,2,4-OXADIAZOLES FROM α-HYDROXY ESTERS AND AMIDOXIMES UNDER SOLVENT-FREE CONDITIONS

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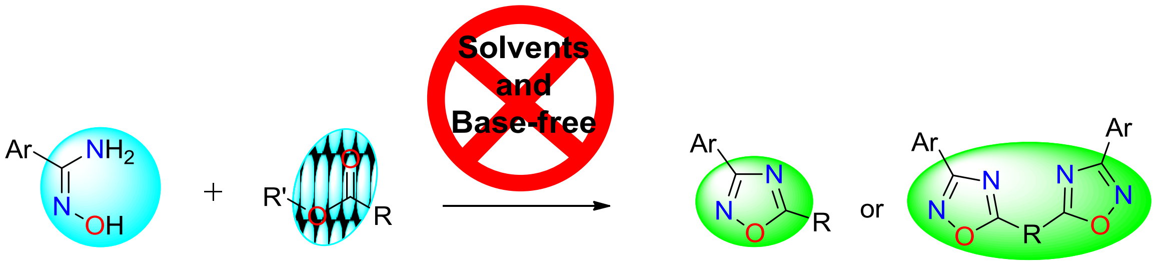
ABSTRACT

The present study aimed the synthesis and characterization of 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles (5a-d, 6a-d, 7a/d, 8a-d and 9a-c). The 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles were synthesized by treatment of arylamidoxime 1a-d with α-hydroxy esters for 4 hours without any solvent and in the absence of a base. The reaction was monitored by thin layer chromatography (TLC). The heterocycles 5a-d, 6a-d, 7a/d, 8a-d and 9a-c were obtained in moderate and good yields (16-76%). The minor yield of the product (16-55%) probably due to the steric hindrance. The presences of electron-withdrawing and electron-donating groups attached to the *para* position of arylamidoximes were well tolerated by the reaction. The products were characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and all compounds were in full agreement with the proposed structure. For instance, IR absorptions at 1593 (C=N) and 1473 cm^{-1} (C–O) were obtained for 3-phenyl-5-(1-hydroxyethyl)-1,2,4-oxadiazoles (5a). ^{1}H NMR spectra showed absorption of methine proton of C–OH at δ 5.16. Signals of the methyl groups for 5a-d appeared as doublets at 1.69 ppm (*J* = 6.6 Hz). The characteristic signals for NCO and NCN in ^{13}C NMR at 180.9 and 168.1 ppm further identified oxadiazole moiety in 5a. With respect to compounds 6a-d the ^{1}H NMR spectra showed a triplet at 5.33 ppm (*J*= 4.5 Hz) for methine proton and a doublet at 3.71 ppm (*J*=4.5 Hz) for the methylene groups. The compounds 8a-d showed an singlet at 3.76 ppm due to methyl groups of ester groups. Signals of the CH protons for 7ad appeared as singlet at 6.93 and 5.50 ppm. All other proton signals are observed in their usual resonance areas. On the other hand, the compounds 8a-d showed a singlet at 3.76 ppm due to methyl groups of ester groups.

Keywords: Amidoxime; 1,2,4-oxadiazoles; α-hydroxy esters; solvent-free.

GRAPHICAL ABSTRACT



17 examples
up to 73% yield

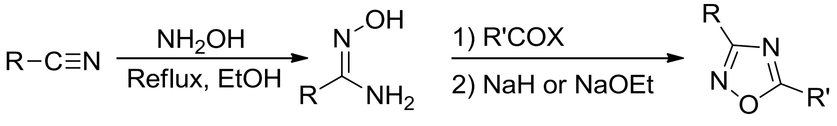
THIS WORK DESCRIBES A SYNTHESIS OF 3-ARYL-5-HYDROXYALKYL-1,2,4-OXADIAZOLES IN THE ABSENCE OF SOLVENT AND BASE.

1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

The azoles are the five-membered heterocyclic compounds with two or three nitrogen atoms, constituting a large group of organic substances they have long been targeted for their use as therapeutic agents [1]. 1,2,4-oxadiazoles are a part of the azole family, containing two nitrogen atoms, two carbon and one oxygen atom in the ring. 1,2,4-oxadiazole containing these compounds have attracted great attention due to their applications in material chemistry and therapeutics [2]. The oxadiazole rings occur widely in biologically active synthetic compounds, and have often been used in the design of compounds with improved physicochemical properties and bioavailability, as they are a bioisosteres of esters and amides^2 and a dipeptide mimetic [3]. Compounds with a 1,2,4-ozadiazole nucleus have been suggested as muscarinic agonists [2,4], benzodiazepine agonists [5], dopamine ligants [6], antirhinovirals [2], growth hormone secretagogues [7], histamine H3 antagonists [8], inhibitors of the SH2 domain of tyrosine kinase [9], monoamine oxidase inhibitors [10], serotoninergic (5-HT3) antagonists [11], for their antitrypanosomal activity [12], as b-amyloid imaging agents in Alzheimer's disease [13], for their peptide inhibitory activity [14], for their antihyperglycemic activity [15] and as potential Combretastatin A-4 (CA-4) analogs [16].

They can act as anticonvulsant [17], anti-inflammatory [18,19], antimicrobial [20], antitumoral [21,22] properties as well as inhibitors of human neutrophil elastase [23], and human DNA topoisomerases [24]. More recently, publications have also shown their application in the field of luminescent liquid crystals, materials for optical devices, and as charge-transporters for organic light emitting diodes (OLEDs) [25,26].

In general, 1,2,4-oxadiazoles are synthetized in two steps by *O*-acylation of an amidoxime, which can be easily prepared by reaction of nitriles with hydroxylamine, with an activated carboxylic acid or derivatives (esters, anhydrides and acyl chloride), typically an active *O*-acylamidoxime, followed by cyclodehydration (Scheme 1) [27]. Another way to synthesize 1,2,4-oxadiazoles is based on the 1,3-cycloaddition of *N*-oxides to azomethines, nitriles, and iminoesters. Existing methods of synthesizing 1,2,4-oxadiazoles from carboxylic acid esters require the presence of strong bases, such as NaH or NaOEt, in refluxing THF or EtOH, and generally give low yields [28]. On the other hand, the condensation of carboxylic acid esters and amidoximes in the presence of potassium carbonate can be employed to synthesize a variety of mono-, bis- and tris-oxadiazoles in moderate to excellent yields [29]. In our research, we were interested in a user-friendly synthesis of 1,2,4- oxadiazoles with carboxylic acid esters and amidoximes with good yields.



R = R' = Alkyl or Aryl X = -OR, -OCOR, -Cl

Scheme 1. Synthetic route for the preparation of 1,2,4-oxadiazoles.

Herein we report a favorable synthesis of 5-α-hydroxy-1,2,4-oxadiazoles and bis-oxadiazoles by heating of α-hydroxy esters and an amidoximes without any solvent and in the absence of a base. The synthesis is environmentally friendly.

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY

Material

All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions distilled for purity. Infrared spectra were recorded on a Brucker IFFS66 series Fourier transform spectrophotometer. NMR spectra were recorded with a Varian Unity Plus instrument (300/75 MHz for ^{1}H/^{13}C) spectrometer, using $CDCl_3$ or DMSO as solvent and Me_4Si as the internal standard. Chemical shifts are reported in ppm. Coupling constants are reported in Hz. Thin Layer Chromatography (TLC) was performed using Merck Silica gel 60 F_{254} Plates. Elemental analyses were carried out with a Carlo Erba model 1110 apparatus. The results of the elemental analysis (C, H, N) are within ± 0.4% of the calculated amounts.

General experimental procedure for the synthesis of 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles 5a-d

α-hydroxy esters (0.190g, 1.0 mmol) and amidoxime (0.214g, 5.0 mmol) were mixed in a vial. The mixture reaction was then heated in an oil bath at 105-110 $^{\circ}$C for 4 h. TLC showed completion of the reaction. The resultant mixture was then purified by chromatography on silica gel to produce a pale yellow oil product in good and moderate yield.

General experimental procedure for the synthesis of 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles 6a-d, 7a/d, 8a-d and 9a-c

α-hydroxy esters (0.206g, 1.0 mmol) and amidoxime (0.33g, 2.0 mmol) were mixed in a vial. The reaction mixture was then heated in an oil bath at 110-120 $^{\circ}$C for 5 h when the mixture stopped reacting. Progress of the reaction was monitored by TLC, indicated completion of the reaction. The resultant mixture was then purified by chromatography on silica gel to give product as a white solid in moderate yield.

3-phenyl-5-(1-hydroxyethyl)-1,2,4-oxadiazoles (5a): Pale yellow oil, yield 71%, R_f=0.62 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3415 (O-H), 2926 (C-H), 1593, 1352, 1129, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.13-8.04 (m, 2H, Ph-H), 7.53-7.44 (m, 3H, Ph-H), 5.16 (q, 1H, J= 6.6 Hz); 3.00 (s, 1H, O-H), 1.69 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 181.1, 168.1, 131.3, 128.9, 127.4, 126.2, 63.2, 21.3. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 4.30; N, 14.75. Found: C, 63.13; H, 5.25; N, 14.72.

3-*p*-tolyl-5-(1-hydroxyethyl)-1,2,4-oxadiazoles (5b): Pale yellow oil, yield 73%, R_f=0.51 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3407 (O-H), 2917 (C-H), 1580, 1339, 1138, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, , J = 8.0 Hz Ph-H), 7.40 (m, 3H, Ph-H), 5.15 (q, 1H, J = 6.8 Hz), 2.40 (s, 1H, O-H), 1.67 (d, 3H, J = 6,8 Hz,); ^{13}C NMR ($CDCl_3$): δ 180.6, 167.5, 141.2, 129.1, 126.9, 122.9, 62.6, 21.04, 21.02. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.62; H, 5.89; N, 13.71.

3-*m*-tolyl-5-(1-hydroxyethyl)-1,2,4-oxadiazoles (5c): Pale yellow oil, yield 76%, R_f=0.53 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3394 (O-H), 2957 (C-H), 1569, 1338, 1115, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.86 (m, 2H, Ph-H), 7.35 (m, 2H, Ph-H), 5.18-5.11 (q, 1H, J = 6.6 Hz), 3.70 (s, 1H, O-H), 2.40 (s, 3H, H_3C-Ph), 1.71 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 188.5, 167.8, 138.3, 131.7, 128.4, 127.6, 125.7, 124.1, 62.9, 21.0, 21.0. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.63; H, 5.90; N, 13.69.

3-*o*-tolyl-5-(1-hydroxyethyl)-1,2,4-oxadiazoles (5d): Pale yellow oil, yield 65%, R_f=0.56 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3289 (O-H), 2957 (C-H), 1580, 1339, 1112, 767 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96 (d, J=8.4 Hz, 1H, Ph-H), 7.35-7.23 (m, 3H, Ph-H), 5.25-5.20 (q, 1H, J = 6.9 Hz), 3.25 (s, 1H, O-H), 2.62 (s, 3H, H_3C-Ph), 1.72 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 180.2, 168.9, 138.6, 131.7, 131.0, 130.4, 126.3, 125.9, 63.6, 22.4, 21.7. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.61; H, 5.91; N, 13.68.

1,2-bis-(3-phenyl-1,2,4-oxadiazol-5-yl)-ethanol (6a)*:* Yield 55%; R_f=0.66 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3395, 1596, 1345, 1087, 726 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 7,90 (2H, m), 7.49 (3H, m), 5.51(t ,1H, J= 4.5 Hz), 4.24 (bs, 1H), 3.52 (d, 2H, J=4.5 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 177.5, 175.3, 168.1, 167.8, 131.2, 128.6, 127.1, 125.8, 63.9, 31.9. Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found: C, 64.63; H, 4.21; N, 16.74.

1,2-bis-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)-ethanol (6b): Yield 68%; R_f=0.76 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3303, 1650, 1353, 1075, 738 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.88 (4H, m), 7.24 (4H, m), 5.51 (t ,1H, J= 6.0 Hz), 3.63 (d, 2H, J = 6.0 Hz), 2.41 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 178.0, 175.8, 168.8, 168.5, 142.3, 130.0, 127.8, 123.6, 64.6, 32.6, 22.0. Anal. Calcd for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.31; H, 4.99; N, 15.44.

1,2-bis-(3-*m*-tolyl-1,2,4-oxadiazol-5-yl)-ethanol (6c)*:* Yield 65%; R_f=0.71 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3367, 1575, 1451, 1125, 763 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.85 (2H, m), 7.27 (2H, m), 5.53 (t ,1H, J = 6.0 Hz), 4.72 (bs, 1H), 3.74 (d, 2H, J = 6.0 Hz), 2.43 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 177.4, 175.2, 168.2, 167.9, 138.4, 131.9, 128.5, 127.7, 125.7, 125.0, 124.3, 63.9, 31.9, 20.9. Anal. Calcd for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.28; H, 5.02; N, 15.43.

1,2-bis-(3-*o*-tolyl-1,2,4-oxadiazol-5-yl)-ethanol (6d)*:* Yield 51%; R_f=0.72 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3350, 1577, 1362, 1103, 721 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.77 (2H, m), 7.26 (2H, m), 5.52 (t ,1H, *J* = 6.0 Hz), 3.56 (d, 2H, *J* = 6.0 Hz), 2.42 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 177.3, 175.1, 168.0, 167.8, 138.3, 131.8, 128.4, 127.6, 125.4, 124.2, 63.8, 31.8, 20.9. Anal. Calcd for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.32; H, 5.00; N, 15.47.

1,2-bis-(3-phenyl-1,2,4-oxadiazol-5-yl)-ethane-1,2-diol (7a)*:* Yield 56%; R_f=0.71 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3350, 1577, 1362, 1103, 721 cm^{-1}; ^1H NMR (300MHz, DMSO-d_6) δ 8.00 (2H, m), 7.54 (3H, m), 6.95 (s ,1H, CH), 5.50 (s, 1H, CH); ^{13}C NMR (75MHz, DMSO-d_6) δ 178.7, 167.7, 131.8, 129.5, 127.2, 126.2, 69.2, 68.2. Anal. Calcd for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.03; N, 15.99. Found: C, 61.69; H, 4.01; N, 15.97.

1,2-bis-(3-*o*-tolyl-1,2,4-oxadiazol-5-yl)-ethane-1,2-diol (7d): Yield 37%; R_f=0.67 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3350, 1577, 1362, 1103, 721 cm^{-1}; ^1H NMR (300MHz, DMSO-d_6) δ 7.77 (2H, m), 7.48 (2H, m), 6.76 (s ,1H, CH), 5.50 (s, 1H, CH), 2.44 (s, 3H); ^{13}C NMR (75MHz, DMSO-d_6) δ 178.0, 167.3, 138.4, 131.9, 128.8, 127.1, 126.3, 123.9, 68.7, 20.52. Anal. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.78; N, 14.81. Found: C, 63.49; H, 4.77; N, 14.82.

Methyl 3-hydroxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-propanoate (8a): Yield 30%; R_f=0.45 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3395, 1752, 1597, 1344, 1089, 726 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 8.04 (2H, m), 7.50 (3H, m), 5.48 (s ,1H), 3.76 (s, 3H), 3.06 (m, 2H, *J* = 6.3 Hz), 1.54 (s, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 180.1, 169.8, 167.2, 131.4, 129.1. 126.7, 125.8, 61.9, 51.4, 21,5. Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.04; H, 4.89; N, 11.27.

Methyl 3-hydroxy-3-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)-propanoate (8b): Yield 33%; R_f=0.50 (dichlromethane–ethyl acetate, 9:1);IR v_{max} (KBr): 3404, 1752, 1595, 1446, 1361, 1048, 758 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 8.00 (2H, m), 7.42 (3H, m), 5.49 (t ,1H, *J* = 5.1 Hz), 3.76 (s, 3H), 3.04 (m, 2H, J=5.1 Hz), 2.48 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 177.9, 170.8, 167.9, 141.3, 129.1, 127.0, 123.0, 63.3, 51.9, 38.4, 21.1. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.52; H, 5.37; N, 10.69.

Methyl 3-hydroxy-3-(3-*m*-tolyl-1,2,4-oxadiazol-5-yl)-propanoate (8c): Yield 33%; R_f=0.51 (dichlromethane–ethyl acetate, 9:1);IR v_{max} (KBr): 3242, 1734, 1570, 1450, 1340, 1037, 716 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.88 (2H, m), 7.44 (2H, m), 5.48 (t ,1H, *J* = 3.6 Hz), 3.75 (s, 3H), 3.04 (m, 2H, J=5.1 Hz), 2.48 (s, 3H); ^{13}C NMR (75MHz, $DMSO_d$) δ 178.1, 170.9, 168.1, 138.4, 131.9; 128.4. 127.8, 125.9, 124.3, 63.4, 52.0, 38.6, 20.9. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.55; H, 5.39; N, 10.67.

Methyl 3-hydroxy-3-(3-*o*-tolyl-1,2,4-oxadiazol-5-yl)-propanoate (8d): Yield 16%; R_f=0.50 (dichlromethane–ethyl acetate, 9:1);IR v_{max} (KBr): 3406, 1738, 1595, 1476, 1337, 1048, 751 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.4 Hz), 7.44 (2H, m, *J* = 8.4 Hz), 5.48 (t ,1H, *J* = 5.1 Hz), 3.75 (s, 3H), 3.04 (m, 2H, *J* = 4.8 Hz), 2.48 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 180.5, 170.3, 167.8, 166.4, 139.0, 132.6, 129.5, 127.7, 126.2, 124.5, 62.5, 51.9, 30.3, 21.2. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.53; H, 5.36; N, 10.69.

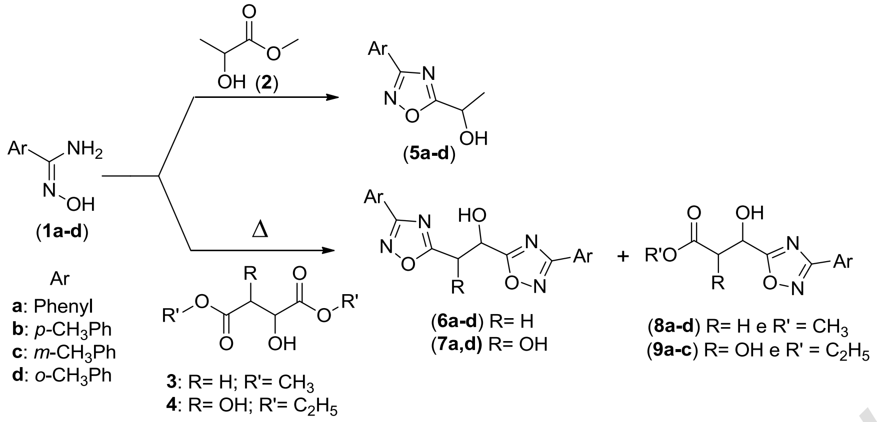
Ethyl 2,3-dihydroxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-propanoate (9a): Yield 16%; R_f=0.40 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3392, 1742, 1570, 1446, 1368, 1089, 706 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.48 (2H, m), 5.42 (d ,1H, *J* = 1,8 Hz), 4.74 (d ,1H, *J* = 1,8 Hz), 4.25 (m, 2H, *J* = 5.4 Hz), 3.75 (s, 2H), 1.25 (m, 3H, *J* = 5.4 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 171.5, 170.9, 168.3, 131.4, 128.9. 127.6, 126.2, 72.3, 68.7, 63.0, 14.1. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.10; H, 5.06; N, 10.08.

Ethyl 2,3-dihydroxy-3-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)-propanoate (9b): Yield 31%; R_f=0.32 (dichlromethane–ethyl acetate, 9:1);IR v_{max} (KBr): 3357, 1737, 1581, 1456, 1353, 1080, 729 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.26 (2H, m), 5.42 (d ,1H, *J* = 2.4 Hz), 4.68 (d,1H, *J* = 2.4 Hz), 4.25 (m, 2H, *J* = 6.9 Hz), 3.24 (s, 2H), 2.44 (s, 3H), 1.25 (m, 3H, *J* = 6.9 Hz); ^{13}C NMR (75MHz, $DMSO_d$) δ 177.5, 171.9, 171.3, 142.1, 129.9, 127.8. 123.7, 72.3, 69.0, 62.8, 21.9, 14.4. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.12; H, 5.08; N, 10.06.

Ethyl 2,3-dihydroxy-3-(3-*m*-tolyl-1,2,4-oxadiazol-5-yl)-propanoate (9c): Yield 28%; R_f=0.41 (dichlromethane–ethyl acetate, 9:1); IR v_{max} (KBr): 3356, 1742, 1570, 1446, 1368, 1089, 706 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.25 (2H, m), 5.50 (d ,1H, *J* = 1.8 Hz), 4.72 (d ,1H, *J* = 1.8Hz), 4.33 (m, 2H, *J* = 5.1 Hz), 3.50 (s, 2H), 2.30 (s, 3H), 1.23 (m, 3H, *J* = 5.1Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 177.3, 171.6, 170.9, 168.3, 138.7, 132.3, 128.8, 128.1, 126.0, 124.7, 72.0, 68.9, 62.5, 21.2, 14.1. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.09; H, 5.07; N, 10.06.

3. RESULTS AND DISCUSSION

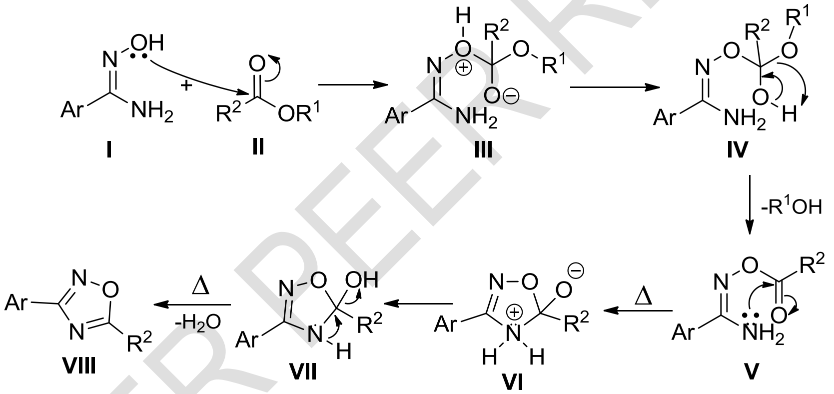
The precursors arylamidoximes **1a-d** could be easily synthesized in moderate and excellent yields (31- 89%) by reaction of nitrile and hydroxylamine hydrochloride in water at 25ºC [30, 31]. The general synthetic strategy for the synthesis of 1,2,4-oxadiazoles an bis-1,2,4-oxadiazoles is illustrated in Scheme 2.



Scheme 2. Synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acid esters.

The 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles were synthesized by treatment of arylamidoxime **1a-d** with α-hydroxy esters for 4 hours without any solvent and in the absence of a base. The reaction was monitored by thin layer chromatography (TLC). The heterocycles **5a-d**, **6a-d, 7a/d, 8a-d and 9a-c** were obtained in moderate and good yields (16-76%). As shown in Scheme 2, the condensation of carboxylic acid esters with amidoximes under simples and solvent-free conditions yielded bis-oxadiazoles (**6a-d and 7a/d)** and 1,2,4-oxadiazoles **5a-d**, **8a-d and 9a-c**.

The scope and generality of this process is illustrated by a series of seventeen compounds and the results are presented in Table 1 below. Based on these data, we proposed the following mechanism for the formation of 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles (**5a-d**, **6a-d and 7a/d).**



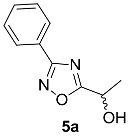
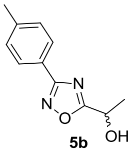
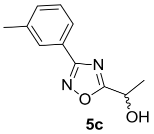
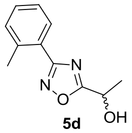
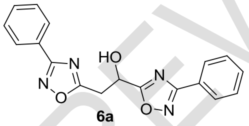
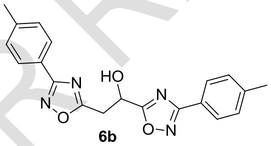
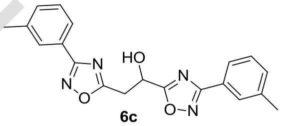
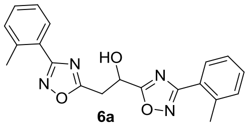
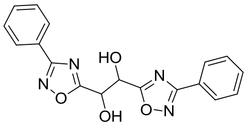
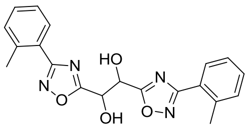
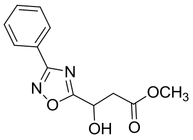
Scheme 3. Plausible mechanism for the formation of 1,2,4-oxadiazoles.

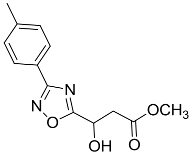
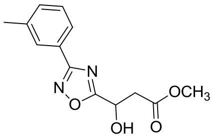
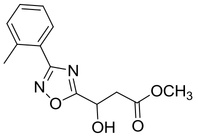
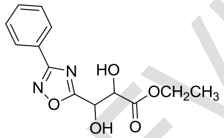
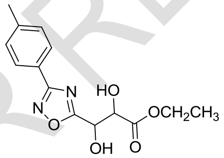
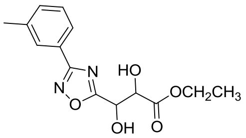
The oxygen of the amidoxime then performs nucleophilic attack on the ester carbonyl, to furnish an unstable tetrahedral species (III and IV) with subsequent loss of alcohol to give V. Upon restoration of the double bond, C = O (V) is the output of alcohol formation of carbonic acid and O-acylated amidoxime (VI), which, in turn, undergo intramolecular nucleophilic attack for the formation of intermediate (VII). At high temperatures there is an output of a molecule of water and formation of the double bond between N-4 and C-5 and therefore of the 1,2,4-oxadiazole ring.

We found the reaction presented an ample scope of applications furnishing the desired products in moderate to good yield (Table 1). We observed that arylamidoximes containing methyl group attached to the *meta* and *para* position reacted similarly, during the reaction with orto tolyl-amidoxime. This furnished a minor yield of the product (16-55%) probably due to the steric hindrance. The presences of electron-withdrawing and electron-donating groups attached to the *para* position of arylamidoximes were well tolerated by the reaction.

Table 1. Synthesis 1,2,4-oxadiazole derivatives **5a-d**, **8a-d**, **9a-c** and bis-1,2,4-oxadiazoles **6a-d**, **7a/d.**

Entry	α-hydroxy esters	Amidoximes	Products	Yield (%)

1	**2**	**1a**	 **5a**	71
2	**2**	**1b**	 **5b**	73
3	**2**	**1c**	 **5c**	76
4	**2**	**1d**	 **5d**	65
5	**3**	**1a**	 **6a**	55
6	**3**	**1b**	 **6b**	68
7	**3**	**1c**	 **6c**	65
8	**3**	**1d**	 **6a**	51
9	**4**	**1a**	 **7a**	56
10	**4**	**1d**	 **7d**	37
11	**3**	**1a**	 **8a**	30

12	**3**	**1b**	 **8b**	20
13	**3**	**1c**	 **8c**	25
14	**3**	**1d**	 **8d**	33
15	**4**	**1a**	 **9a**	16
16	**4**	**1b**	 **9b**	28
17	**4**	**1c**	 **9c**	31

The products were characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and all compounds were in full agreement with the proposed structure. For instance, IR absorptions at 1593 (C=N) and 1473 cm^{-1} (C–O) were obtained for 3-phenyl-5-(1-hydroxyethyl)-1,2,4-oxadiazoles (**5a**). ^{1}H NMR spectra showed absorption of methine proton of C–OH at δ 5.16. Signals of the methyl groups for **5a-d** appeared as doublets at 1.69 ppm (J = 6.6 Hz). The characteristic signals for NCO and NCN in ^{13}C NMR at 180.9 and 168.1 ppm further identified oxadiazole moiety in **5a**. With respect to compounds 6a-d the ^{1}H NMR spectra showed a triplet at 5.33 ppm (J= 4.5 Hz) for methine proton and a doublet at 3.71 ppm (J=4.5 Hz) for the methylene groups. The compounds **8a-d** showed an singlet at 3.76 ppm due to methyl groups of ester groups. Signals of the CH protons for **7ad** appeared as singlet at 6.93 and 5.50 ppm. All other proton signals are observed in their usual resonance areas. On the other hand, the compounds **8a-d** showed a singlet at 3.76 ppm due to methyl groups of ester groups.

4. CONCLUSION

In summary, we report here on a convenient synthesis of 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles from readily available α-hydroxy esters and arylamidoximes without any solvent and in the absence of a base. The final products were obtained after four hours in moderate to good yields.

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COMPETING INTERESTS

The authors declare no conflict of interest.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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