Research Article

Synthesis of New 3-phenyl-5-(3-phenylisoxazole-5-yl) -1,2,4-oxadiazoles

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ABSTRACT

A new series of 3-phenyl-5-(3-phenylisoxazole-5-yl)-1,2,4-oxadiazole **(6a-l)** were synthesized by the reaction of ethyl-3-phenyl isoxazole-5-carbboxylates **(4a-c)** and amide oximes **(5a-g)**. The products were purified by column chromatography and their structures were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

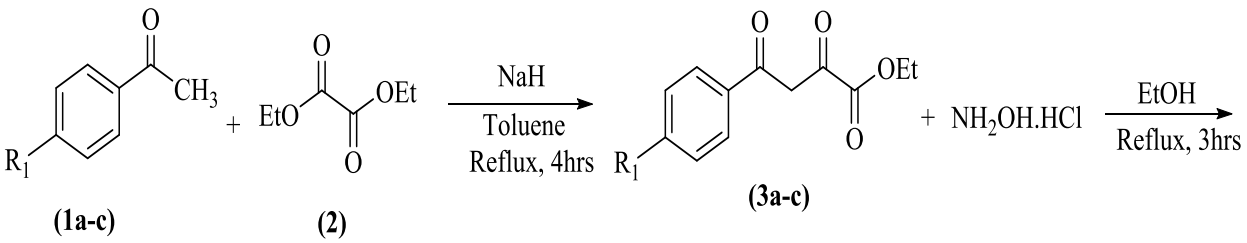
Keywords: 1,2,4-Oxadiazole, 3-Phenyl isoxazole-5-carbboxylates, Amide oximes.

INTRODUCTION

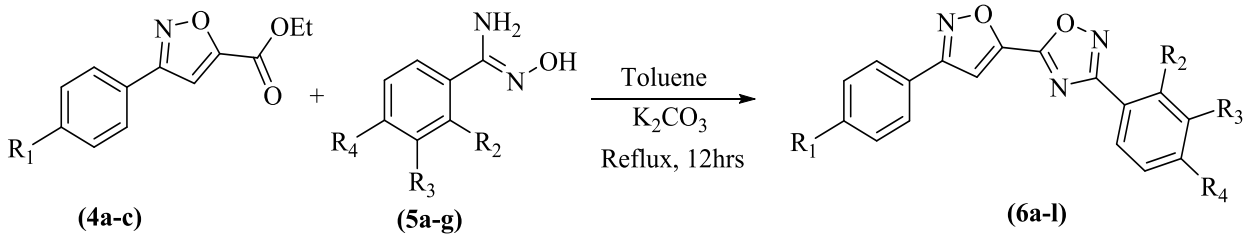
1,2,4-oxadaizoles are a class of important of heterocycles which have been well documented throughout the literature due to their biological significance. The 1,2,4-Oxadaizoles have often been used as bioisosters of esters, they are present in various biologically active compounds, such as benzodiazepine receptor ligands, muscarine receptor agonists and 5-HT3 receptor antagonists[1]. 1,2,4-oxadiazole derivatives posseses human tryptase inhibitory activity[2], anti-infammatory[3], antitumor[4] and antifungal activities[5]. Biologically relevant compounds containing the 1,2,4-oxadiazole moiety also includes HIV integrase inhibitor[6], antituberculostatic agents[7], antikinetoplastid agents[8] and dopamine ligands[9]. In the present article, we report the synthesis of novel 3-phenyl-5-(3-phenylisoxazole-5-yl)-1,2,4-oxadiazole derivatives.

RESULTS AND DISCUSSIONS

Synthesis of 3-phenyl-5-(3-phenylisoxazole-5-yl)-1,2,4-oxadiazole (6a-l): The reaction of acetophenones **(1a-c)** with diethyl oxalate **(2)** in the presence of sodium hydride and toluene as a solvent results ethyl-2,4-dioxo-4-phenylbutanoates **(3a-c)**. These ethyl-2,4-dioxo-4-phenyl butanoates on reaction with hydroxylamine hydrochloride in ethanol as a solvent yields ethyl-3-phenyl isoxazole-5-carbboxylates **(4a-c)**. These ethyl-3-phenyl isoxazole-5-carbboxylates **(4a-c)** on reaction with amide oximes **(5a-g)** which are prepared from corresponding amines, in toluene and potassium carbonate as base affords title **(6a-l)** compounds in quantative yields.



(1a-c) (2) (3a-c)



(4a-c) (5a-g) (6a-l)

In the IR spectrum **6a**, peaks were observed at 2245cm^{-1}(C=N),1608, 1448cm^{-1}(C=C), 765, 680cm^{-1}(mono substituted benzene) 742, 675cm^{-1}(mono substituted benzene). In the ^{1}H-NMR of spectrum **6a,** the newly formed 3-phenyl-1,2,4-oxadiazole protons of H-2''',6''' appeared as a multiplet at δ 8.20-8.18, H-3,4,5,3''',4''',5''' appeared as multiplet at δ 7.54-7.51, H-2,6 observed as multiplet in the range δ 7.89-7.86 and proton H-4' appeared as a singlet. In the ^{13}C-NMR spectrum of **6a,** the carbon signal assignments are as follows 172.1, 168.8, 168.1, 151.5, 132.4, 131.7, 129.8, 127.6, 126.4, 126.1, 125.9, and 100.9. In the mass spectrum of **6a**, molecular ion peak was observed at m/z 290 [M+H].

EXPERIMENTAL SECTION

Chemistry

All reactions were carried out under nitrogen atmosphere in oven-dried glassware with magnetic stirring**.** All the chemicals and solvents were purchased from Sd fine chemicals, Bombay, India. Solvents were purified and dried according to the standard procedures. Silica gel (60–120 mesh) for column chromatography was purchased from M/s Acme Synthetic Chemicals (Mumbai, India) and pre-coated TLC plates (Silica gel 60F254) were purchased from Merck (Darmstadt, Germany). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 400 and 100 MHz, respectively, and TMS was used as an internal standard. Chemical shifts relative to TMS as internal standards were given as δ values in ppm. Mass spectra were recorded using electron spray ionization on Waters e2695 Separators module (Waters, Milford, MA, USA) mass spectrometer. IR spectra were recorded on a Fourier transform (FT-IR), USA (Perkin-Elmer model 337) instrument. The melting points were determined on a Barnstead Electro Thermal 9200 Instrument.

1) General procedure for the synthesis of ethyl-2,4-dioxo-4-phenylbutanoates (3a-c)

To a stirred solution of Acetophenone **(1a-c)** and diethyl oxalate **(2)** in anhydrous THF was added sodiumhydride portion wise for 30 minutes under nitrogen atmosphere. Then the reaction mixture was stirred for 2h at 0^{o}C, progress of the reaction was monitored by TLC, on completion of the starting material, it is quenched by the addition of cooled 2N HCl at 0^{o}C and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and then concentrated on reducer pressure to obtain crude which is further purified by column chromatography using 10% ethyl acetate-hexane mixture to gave ethyl 3-oxo-3-phenylpropanoate **(3a-c).**[10-12]

2) Synthesis of ethyl-3-phenyl isoxazole-5-carbboxylates (4a-c)

To a stirred solution of ethyl 2,4-dioxo-4-phenylbutanoate **(3a-c)** in ethanol was added hydroxylamine hydrochloride under nitrogen atmosphere. Then the reaction mixture was refluxed for 3h, progress of the reaction was monitored by TLC, on completion of starting material most of the solvent was removed and the crude was dissolved in EtOAc, washed with water followed by saturated sodium chloride. The combined organic layers were dried over anhydrous sodium sulphate and then concentrated on reducer pressure to give ethyl 3-phenylisoxazole-5-carboxylate as a white solid **(4a-c).**[10-12] As the product is obtained in pure form . I have proceded to the next step without any further purification.

3) Synthesis of amide oximes (5a-g)

To a mixture of phenylacetonitrile (6.3g, 53.8mmol) in EtOH (60 mL), $NH_2OH.HCl$ (7.5g, 107.6 mmol) and Et_3N (10.8g, 107.6 mmol) were added and refluxed for 3h. After completion of the reaction, EtOH was removed completely. To the residue water (100 mL) was added and extracted into ethylacetate (100 mL), dried over Na_2SO_4 and concentrated to yield the amide oxime **(5a-g).**

4) Synthesis of 3-phenyl-5-(3-phenylisoxazole-5-yl)-1,2,4-oxadiazole (6a-l) To a stirred solution of ethyl 3-phenylisoxazole-5-carboxylate **(4a-c)** (1.2mmol) in toluene (30ml), potassium carbonate (0.5g, 3.62mmol) and N'-hydroxybenzimidamides **(5a-g)** (1.8mmol)

were added and refluxed for 14 hours. After completion of the reaction by TLC monitoring, the reaction mixture was concentrated under rotatory evaporator. Water (50ml) was added and extracted with ethylacetate (3x50ml). The organic layer was washed with water and dried over sodium sulphate. The organic layer was concentrated on rotary evaporator and purified by column chromatography using (silica gel 60-120 mesh) petether:ethylacetate as eluent to get the pure title compound **(6a-l)**.

i) 3-Phenyl-5-(3-phenylisoxazole-5-yl)-1,2,4-oxadiazole (6a)

White solid, m.p. 80^{0}C. Yield 52%. IR (KBr) cm^{-1}: 1608, 1448, 1346, 1028, 943, 765, 742, 680 and 675. ^{1}H-NMR($CDCl_3$, 400MHz): δ 8.20 – 8.18 (m, H-2‴, 6‴, 2H), 7.89 – 7.86 (m, H-2,6, 2H), 7.54 – 7.51 (m, H-3,4,5,3‴,4‴,5‴, 6H), 7.17 (s, H-4', 1H). ^{13}C-NMR ($CDCl_3$, 100MHz):δ 172.1, 168.8, 168.1, 151.5, 132.4, 131.7, 129.8, 127.6, 126.4, 126.1, 125.9, 100.9. . MASS (ESIMS): 290 [M+H].

ii) 3-(2-Chlorophenyl)-5-(3-phenylisoxazol-5-yl)-1,2,4-oxadiazole (6b)

White solid, m.p. 88^{0}C. Yield 60%. IR (KBr) cm^{-1}: 1618, 1442, 1327, 1082, 947, 758, and 678. ^{1}H-NMR($CDCl_3$, 400MHz): δ 8.07 (ddd, J = 9.7, 7.7, 4.0Hz, 3H), 7.94 (s, 1H), 7.76 (d, J = 8.0Hz, 1H), 7.70 (ddd, J = 9.0, 7.2, 1.5Hz, 1H), 7.63-7.60 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100MHz): δ 172.1, 168.3, 168.1, 166.7, 151.5, 137.2, 136.3, 131.8, 130.0, 129.8, 129.7, 129.4, 129.2, 126.4, 100.9. MASS (ESIMS): 324[M+H], 326 [M+H+2].

iii) 3-(4-Chlorophenyl)-5-(3-phenylisoxazol-5-yl)-1,2,4-oxadiazole (6c)

White solid, m.p. 73^{0}C. Yield 48%. IR (KBr) cm^{-1}: 1643, 1606, 1381, 1332, 1093, 941. ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.16-8.10 (m, H-2‴,6‴, 2H), 8.05-8.01 (m, H-2,6, 2H), 7.91 (s, H-4', 1H), 7.73-7.59 (m, H-3,4,5,3‴,5‴, 5H). MASS (ESIMS): 324[M+H], 326 [M+H+2].

iv) 3-(3-Chlorophenyl)-5-(3-phenylisoxazol-5-yl)-1,2,4-oxadiazole (6d)

White solid, m.p. 86^{0}C. Yield 62%. IR (KBr) cm^{-1}: 1612, 1577, 1342, 1307, 1022, 943. 1H NMR (400MHz, dmso) δ 8.07 (s, H-2‴,1H), 8.06 – 8.01 (m, H-4‴,5‴,6‴, 3H), 7.93 (s, H-4', 1H), 7.74 (d, J = 8.1 Hz, H-2, 1H), 7.65 (dd, J = 14.8, 6.6 Hz, H-6, 1H), 7.59 (d, J = 3.9 Hz, H-3,4,5, 3H). ^{13}C NMR (101 MHz, dmso) δ 172.1, 168.5, 167.7, 151.6, 134.5, 132.3, 132.0, 131.8, 129.9, 127.8, 127.2, 126.4, 126.3, 126.1, 101.2. MASS (ESIMS): 324[M+H], 326 [M+H+2].

v) 5-(3-Phenylisoxazol-5-yl)-3-(o-tolyl)-1,2,4-oxadiazole (6e)

White solid, m.p. 77^{0}C. Yield 51%.IR (KBr) cm^{-1}: 1620. 1604, 1564, 1448, 1338, 1244, 945. 1H NMR (400MHz, dmso) δ 8.08 – 7.97 (m, H-2,6,6‴, 3H), 7.89 (s, 1H), 7.59 (dd, J = 5.0, 1.3 Hz, H-3,4,5, 3H), 7.52 (t, J = 7.2 Hz, H-5‴, 1H), 7.44 (dd, J = 13.8, 7.0 Hz, H-3‴,4‴, 2H), 2.61 (s, CH_3, 3H). ^{13}C-NMR (101 MHz, dmso) δ 172.1, 169.4, 167.1, 151.6, 138.2, 132.0, 131.8, 131.7, 130.3, 129.8, 126.8, 126.4, 126.1, 125.2, 100.9, 22.1. MASS (ESIMS): 304 [M+H].

vi) 3-(4-Bromophenyl)-5-(3-phenylisoxazol-5-yl)-1,2,4-oxadiazole (6f)

White solid, m.p. 73^{0}C. Yield 68%. IR (KBr) cm^{-1}: 1597, 1564, 1444, 1404, 1382, 1332, 1238, 937. ^{1}H-NMR (400 MHz, dmso) δ 8.02 (d, J = 8.0 Hz, H-2‴,3‴,5‴,6‴, 4H), 7.91 (s, H-4', 1H), 7.83 (d, J = 8.3 Hz, H-2,6, 2H), 7.59 (d, J = 3.7 Hz, H-3,4,5, 3H). ^{13}C-NMR (101 MHz, dmso) δ 172.1, 168.3, 168.2, 151.5, 133.0, 131.8, 129.9, 129.6, 126.4, 126.1, 126.1, 125.1, 100.9. MASS (ESIMS): 368[M+H], 370[M+H+2].

vii) 3-(2-Fluorophenyl)-5-(3-phenylisoxazol-5-yl)-1,2,4-oxadiazole (6g)

White solid, m.p. 82^{0}C. Yield 74%. IR (KBr) cm^{-1}: 1612, 1570, 1485, 1450, 143, 1390, 1334, 1230, 758.1H-NMR (400 MHz, dmso) δ 8.10 (t, J = 7.1 Hz, H-6‴, 1H), 8.05 – 8.00 (m, H-2,6, 2H), 7.88 (s, H-4', 1H), 7.69 (dd, J = 12.8, 6.5 Hz, H-3‴, 1H), 7.57 (d, J = 3.8 Hz, H-3,4,5, 3H), 7.47 (dd, J = 17.9, 9.9 Hz, H-4‴,5‴, 2H). ^{13}C-NMR (101 MHz, dmso) δ 172.1, 167.7, 165.7, 165.6, 161.6, 159.0, 151.4, 134.5, 134.4, 131.8, 131.0, 129.8, 126.4, 126.1, 125.7, 125.7, 117.5, 117.3, 114.1, 114.0, 100.9. MASS (ESIMS): 308[M+H].

viii) 3-(3-Chlorophenyl)-5-(3-(4-methoxyphenyl)isoxazol-5-yl)-1,2,4-oxadiazole (6h)

IR (KBr) cm^{-1} 1604, 1500, 1436, 1255, 1164, 1009, 933. ^{1}H-NMR (400 MHz, dmso) δ 8.07 (d, J = 7.7 Hz, H-2‴,6‴, 2H), 7.98 (d, J = 8.6 Hz, H-2,6, 2H), 7.77 (s, H-4', 1H), 7.74 (d, J = 8.0 Hz, H-4‴, 1H), 7.66 (t, J = 7.7 Hz, H-5‴, 1H), 7.14 (d, J = 8.6 Hz, H-3,5, 2H), 3.84 (s, OCH_3, 3H). ^{13}C-NMR (101 MHz, dmso) δ 172.2, 168.6, 167.8, 161.9, 151.3, 134.5, 132.3, 132.0, 128.3, 127.9, 127.2, 126.3, 118.7, 115.3, 99.4, 55.9. . MASS (ESIMS): 354[M+H], 356[M+H+2].

ix) 5-(3-(4-Methoxyphenyl)isoxazol-5-yl)-3-(o-tolyl)-1,2,4-oxadiazole (6i)

White solid, m.p. 89^{0}C. Yield 61%IR (KBr) cm$^-$ 1: 1614, 1608, 1514, 1448, 1344, 1263, 1184, 1155, 1018, 945. 1H-NMR (400 MHz, dmso) δ 7.98 (dd, J = 11.9, 8.5 Hz, H-4‴,5‴,6‴, 3H), 7.71 (s, H-4', 1H), 7.54 – 7.47 (m, H-3‴, 1H), 7.43 (dd, J = 13.5, 6.9 Hz, H-2,6, 2H), 7.12 (d, J = 8.6 Hz, H-3,5, 2H), 3.83 (s, OCH_3, 3H), 2.60 (s, CH_3, 3H). ^{13}C-NMR (101 MHz, dmso) δ 172.1, 169.3, 167.2, 161.9, 151.4, 138.2, 132.0, 131.7, 130.2, 128.2, 126.8, 125.2, 118.8, 115.2, 99.3, 56.1, 22.0. . MASS (ESIMS): 334[M+H].

x) 3-(4-Bromophenyl)-5-(3-(4-methoxyphenyl)isoxazol-5-yl)-1,2,4-oxadiazole (6j)

White solid, m.p. 89^{0}C. Yield 64%. IR (KBr) cm^{-1}: 1614, 1600, 1506, 1473, 1452, 1415, 1263, 1182, 1134, 1016, 829, 756. 1H-NMR (400 MHz, dmso) δ 7.98 (dd, J = 11.9, 8.5 Hz, H-2‴,3‴,5‴,6‴,4H), 7.71 (s, H-4', 1H), 7.43 (dd, J = 13.5, 6.9 Hz, H-2, 6, 2H), 7.12 (d, J = 8.6 Hz, H-3,5, 2H), 3.83 (s, OCH_3, 3H). ^{13}C NMR (100 MHz, dmso) δ 172.2, 168.4, 168.1, 161.9, 151.4, 133.0, 129.6, 128.2, 126.1, 125.1, 118.7, 115.3, 99.3, 55.9. MASS (ESIMS): 398[M+H], 400[M+H+2].

CONCLUSION

We have synthesized novel 3-phenyl-5-(3-phenylisoxazole-5-yl)-1,2,4-oxadiazoles from simple commercially available starting materials.

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