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A simple and efficient procedure for synthesis of optically active 1,3,4-oxadiazole derivatives containing L-amino acid moieties

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Some new unsymmetrical and optically active 2,5-disubstituted 1,3,4-oxadiazoles **5a-j** were efficiently synthesized by cyclization reaction of diacylhydrazides **4a-j**. The synthesis of the title compounds was achieved by the reaction of acyl hydrazides **3a-b** and N-phetaloyl-L-amino acids **1a-e** in the presence of the phosphoroxy chloride ($POCl_3$) as an anhydrous reagent.

Key Words: N-phetaloyl-L-amino acid, 1,3,4-oxadiazole, diacylhydrazide, pyridoyl hydrazide, phosphoroxy chloride

Introduction

The replacement of acid and ester functionality in medicinal chemistry continues to be a popular strategy in the search for compounds with superior pharmacokinetic profiles. In particular, 1,3,4-oxadiazole rings have been of interest to medicinal chemists for many years, because of their antimicrobial,[1] antimitotic,[2] anti-inflammatory,[3] anticonvulsant,[4] and antihepatitis B[5] activities. In addition to their utility as bioactive molecules, 1,3,4-oxadiazoles are useful intermediates for organic synthesis.[6] Consequently, the synthesis of compounds containing this heterocycle core has attracted considerable attention and a wide variety of methods have been used for its assembly. By far the most common synthetic method involves the dehydrative cyclization of diacylhydrazides, usually with strongly acidic reagents such as thionyl chloride,[7] phosphorus pentoxide,[8] polyphosphoric acid,[9] and sulfuric acid.[10] More recently, however, several methods have been developed using

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essentially neutral conditions and cyclization mediators such as Tf_2O[11] and HMDS/TBAF,[12] as well as solid supported cyclization reagents.[13] One-pot synthesis of 1,3,4-oxadiazoles from hydrazine and carboxylic acids has also been reported.[14] Another synthetic route for the preparation of these compounds is the acylation of tetrazoles.[15]

This paper therefore describes the synthesis of oxadiazole derivatives containing L-amino acid moieties attached to the C_2 of the heterocyclic ring, with the hope to obtain compounds with better biological activities.

Experimental

Melting points were determined using an electrothermal digital apparatus and are uncorrected. The purity of compounds was checked by thin layer chromatography (TLC) using EtOH/*n*-hexane (1:1 v/v) as an eluent. IR spectra were prepared on a Galaxy series FT-IR 5000 spectrophotometer using KBr discs. NMR spectra were recorded on a Bruker spectrophotometer (300 MHz) in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. Specific rotations were measured by using an A-Kruse polarimeter. Microanalyses were performed on a Vario EL III elemental analyzer.

General procedure for synthesis of N′-(2-(1,3-dioxoisoindolin-2-yl) acyl) hydrazide 4(a-j):

N-phetaloyl-L-amino acylchoride **2a-e** (5 mmol) and pyridoyl hydrazide **3a-b** (5 mmol) were added to a flask containing 10 mL of N,N-dimethyl acetamide (DMAc). The mixture was allowed to react at room temperature for 5 h. After the reaction was completed, the product was precipitated from distillated water (30 mL). The crude product was filtered, washed with water, dried, and recrystallized from EtOH to provide **4a-j**.

N′-(2-(1,3-Dioxoisoindolin-2-yl) acetyl) isonicotinohydrazide (4a):

Yield: 55%; mp 263-265 °C; IR (KBr) (ν, cm^{-1}): 3246 (NH), 3041, 2928, 1778 (C=O), 1722 (C=O), 1687 (C=O), 1552, 1421; ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.37 (2H, s, N-CH_2), 7.76 (d, J = 6.0 Hz, 2H, aromatic), 7.84-7.94 (m, 4H, aromatic), 8.75 (d, J = 5.9 Hz, 2H, aromatic), 10.53 (s, 1H, NH), 10.81 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl) acetyl) nicotinohydrazide (4b):

Yield: 65%; mp 253-254 °C; IR (KBr) (ν, cm^{-1}): 3196 (NH), 3039, 2939, 1772 (C=O), 1724 (C=O), 1677 (C=O), 1500, 1415; ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.35 (s, 2H, N-CH_2), 7.56 (b, 1H, aromatic), 7.83 (s, 4H, aromatic), 8.20 (d, J = 7.53 Hz, 1H, aromatic), 8.75 (s, 1H, aromatic), 9.02 (s, 1H, aromatic), 10.49 (s, 1H, NH), 10.78 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl) propanoyl) isonicotinohydrazide (4c):

Yield: 51%; mp 195-198 °C; $[\alpha]_D^{22}$ = -150 (c = 0.2, DMSO); IR (KBr) (ν cm^{-1}): 3202 (NH), 3051, 2943, 1776 (C=O), 1712 (C=O), 1664 (C=O), 1552, 1477; ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.54 (d, J = 7.3 Hz, 3H,

CH_3), 4.90 (q, J = 7.3 Hz, 1H, N-CH), 7.74 (d, J = 5.7 Hz, 2H, aromatic), 7.84-7.94 (m, 4H, aromatic), 8.77 (d, 2H, J = 5.6 Hz, aromatic), 10.36 (s, 1H, NH), 10.81 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl) propanoyl) nicotinohydrazide (4d):

Yield: 63%; mp 181-183 °C; $[\alpha]_D^{22}$ = -110 (c = 0.2, DMSO); IR (KBr) (ν cm^{-1}): 3286 (NH), 2972, 1766 (C=O), 1718 (C=O), 1672 (C=O), 1525; ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.51 (d, J = 7.1 Hz, 3H, CH_3), 4.86 (q, J = 7.0 Hz, 1H, N-CH), 7.51 (b, 1H, aromatic), 7.80 (s, 4H, aromatic), 8.23 (d, J = 7.4 Hz, 1H, aromatic), 8.78 (s, 1H, aromatic), 9.05 (s, 1H, aromatic), 10.30 (s, 1H, NH), 10.79 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl)-3-phenyl propanoyl) isonicotinohydrazide (4e):

Yield: 51%; mp 167-170 °C; $[\alpha]_D^{22}$ = -235 (c = 0.2, DMSO); IR (KBr) (ν cm^{-1}): 3257 (NH), 3028, 1776 (C=O), 1712 (C=O), 1687 (C=O), 1498, 1421; ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.54-3.65 (m, 2H, CH_2), 5.15 (d, d, J = 10.9, 4.1 Hz, 1H, N-CH), 7.20 (s, 5H, aromatic), 7.73 (d, J = 6.1 Hz, 2H, aromatic), 7.80-7.91 (m, 4H, aromatic), 8.77 (d, J = 5.9 Hz, 2H, aromatic), 10.47 (s, 1H, NH), 10.72 (s, 1H, NH).

N′-(2-(1,3-dioxoisoindolin-2-yl)-3-phenyl propanoyl) nicotinohydrazide (4f):

Yield: 58%; mp 176-179 °C; $[\alpha]_D^{22}$ = -103 (c = 0.2, DMSO); IR (KBr) (ν cm^{-1}): 3202 (NH), 3051, 2943, 1776 (C=O), 1712 (C=O), 1687 (C=O), 1552 (C=C), 1477; ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.50-3.63 (m, 2H, CH_2), 5.15 (d, d, J = 11.1, 4.2 Hz, 1H, N-CH), 7.16 (s, 5H, aromatic), 7.55 (b, 1H, aromatic), 7.81 (s, 4H, aromatic), 8.22 (d, J = 7.5 Hz, 1H, aromatic), 8.76 (s, 1H, aromatic), 9.04 (s, 1H, aromatic), 10.43 (s, 1H, NH), 10.69 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl)-3-methyl butanoyl) isonicotinohydrazide (4g):

Yield: 50%; mp 207-209 °C; $[\alpha]_D^{22}$ = -86 (c = 0.2, $CDCl_3$); IR (KBr) (ν cm^{-1}): 3280 (NH), 2982, 1760 (C=O), 1712 (C=O), 1670 (C=O), 1530, 1450 (C=C); ^{1}H-NMR ($CDCl_3$, δ, ppm): 0.81 (d, J = 6.5 Hz, 3H, CH_3), 1.13 (d, J = 6.6 Hz, 3H, CH_3), 2.80-2.85 (m, 1H, CH), 4.56 (d, J = 9.0 Hz, 1H, N-CH), 7.74 (d, J = 4.9 Hz, 2H, aromatic), 7.81 (b, 4H, aromatic), 8.76 (d, J = 5.0 Hz, 2H, aromatic), 10.32 (s, 1H, NH), 10.50 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl)-3-methyl butanoyl) nicotinohydrazide (4h):

Yield: 50%; mp 201-203 °C; $[\alpha]_D^{22}$ = -70 (c = 0.2, $CDCl_3$); IR (KBr) (ν cm^{-1}): 3286 (NH), 2972, 1766 (C=O), 1718 (C=O), 1672 (C=O), 1525, 1450 (C=C); ^{1}H-NMR ($CDCl_3$, δ, ppm): 0.84 (d, J = 6.6 Hz, 3H, CH_3), 1.13 (d, J = 6.7, 3H, CH_3), 2.82-2.89 (m, 1H, CH), 4.47 (d, J = 9.3 Hz, 1H, N-CH), 7.52-7.55 (m, 1H, aromatic), 7.87-7.95 (m, 4H, aromatic), 8.20 (d, J = 6.2 Hz, 1H, aromatic), 8.74 (m, 1H, aromatic), 9.00 (s, 1H, aromatic), 10.30 (s, 1H, NH), 10.60 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl)-4-methyl pentanoyl) isonicotinohydrazide (4i):

Yield: 51%; mp 186-187 °C; $[\alpha]_D^{22}$ = -115 (c = 0.2, $CDCl_3$); IR (KBr) (ν cm^{-1}): 3277 (NH), 2980, 1760 (C=O), 1712 (C=O), 1670 (C=O), 1530, 1450 (C=C); ^{1}H-NMR ($CDCl_3$, δ, ppm): 0.92 (d, J = 4.5 Hz, 3H, CH_3), 0.96 (d, J = 4.5 Hz, 3H, CH_3), 1.25 (m, 1H, CH), 1.94-1.98 (m, 1H, CH_2), 2.30-2.36 (m, 1H, CH_2), 4.95 (d, d, J = 10.6, 5.4 Hz, 1H, N-CH), 7.76 (d, J = 4.8 Hz, 2H, aromatic), 7.84-7.92 (m, 4H, aromatic), 8.74 (d, J = 4.9 Hz, 2H, aromatic), 10.26 (s, 1H, NH), 10.57 (s, 1H, NH).

N′-(2-(1,3-Dioxoisoindolin-2-yl)-4-methyl pentanoyl) nicotinohydrazide (4j):

Yield: 50%; mp 179-181 °C; $[\alpha]_D^{22}$ = -65 (c = 0.2, $CDCl_3$); IR (KBr) (ν cm^{-1}): 3270 (NH), 2985, 1770 (C=O), 1720 (C=O), 1672 (C=O), 1535, 1427 (C=C); ^{1}H-NMR ($CDCl_3$, δ, ppm): 0.93 (d, J = 4.3 Hz, 3H, CH_3), 0.96 (d, J = 4.5 Hz, 3H, CH_3), 1.25 (m, 1H, CH), 1.95-2.00 (m, 1H, CH_2), 2.32-2.39 (m, 1H, CH_2), 4.99 (d, d, J = 10.7, 5.5 Hz, 1H, N-CH), 7.50-7.53 (m, 1H, Aromatic), 7.74-7.81 (m, 4H, aromatic), 8.38 (d, J = 7.3 Hz, 1H, aromatic), 8.81 (s, 1H, aromatic), 9.05 (s, 1H, aromatic), 10.28 (s, 1H, NH), 10.54 (s, 1H, NH).

General procedure for synthesis of 5-[2-(isoindolin-1,3-dione)alkyl]-2-(5-pyridin (3or4)-yl)-1,3,4-oxadiazoles 5a-j:

(A) A solution of diacyl hydrazides **4a-j** (5 mmol) and H_2SO_4 (20 mL) was stirred at room temperature for 24 h. After the reaction was completed, the mixture was slowly added to crushed ice (150 g) with stirring and neutralized with concentrated ammonia. The mixture was allowed to stand overnight; the obtained precipitate was filtered and washed with cold water (200 mL). The compound so obtained was dried and crystallized from EtOH/H_2O to give the pure products **5a-j.**

(B) A mixture of pyridoyl acid hydrazide **3a-b** (10 mmol), N-phetaloyl-L-amino acid **1a-e** (10 mmol), and $POCl_3$ (10 mL) was refluxed for 36 h. The reaction mixture was slowly added to crushed ice with stirring and neutralized with solid potassium carbonate. The mixture was allowed to stand overnight and the resulted precipitate was filtered and washed with cold water (100 mL). The compound so obtained was dried and crystallized from appropriate solvent to give the pure products **5a-j**.

2-[1-(5-Pyridine-4-yl)-1,3,4-oxadiazole-2-yl)methyl] isoindoline-1,3-dione (5a):

A) Yield: 65%; B) yield: 40%. mp 191-192 °C; IR (KBr) (ν cm^{-1}): 3041, 2928, 1772 (C=O), 1722 (C=O), 1605 (C=N), 1535, 1420 (C=C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.18 (s, 2H, N-CH_2), 7.88-7.98 (m, 6H, aromatic), 8.80 (d, J = 3.7 Hz, 2H, aromatic); ^{13}C-NMR (DMSO-d_6, δ, ppm): 32.8, 120.7, 124.0, 130.7, 131.9, 135.3, 151.5, 163.3, 163.6, 167.3. Anal. Calcd. for $C_{16}H_{10}N_4O_3$: C, 62.74; H, 3.29; N, 18.29. Found C, 62.65, H, 3.25, N, 18.24.

2-[1-(5-Pyridine-3-yl)-1,3,4-oxadiazole-2-yl) methyl] isoindoline-1,3-dione (5b):

A) Yield: 52%; B) yield: 38%. mp 176-178 °C; IR (KBr) (ν cm^{-1}): 3043, 2933, 1770 (C=O), 1724 (C=O), 1602 (C=N), 1552, 1465 (C=C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.17 (s, 2H, N-CH_2), 7.60-7.65 (m, 1H,

aromatic), 7.88-7.98 (m, 4H, aromatic), 8.80 (d, J = 4.2 Hz, 1H, aromatic), 9.00 (s, 1H, aromatic), 9.13 (s, 1H, aromatic); ^{13}C-NMR (DMSO-d_6, δ, ppm): 32.8, 120.2, 123.9, 124.8, 131.9, 134.7, 135.3, 147.7, 153.1, 162.8, 163.3, 167.3; Anal. Calcd. for $C_{16}H_{10}N_4O_3$: C, 62.74; H, 3.29; N, 18.29. Found C, 62.44, H, 3.18, N, 18.18.

(*S*)-2-[1-(5-Pyridine-4-yl)-1,3,4-oxadiazole-2-yl) ethyl]isoindoline-1,3-dione (5c):

A) Yield: 50%; B) yield: 36%; mp 166-168 °C; $[\alpha]_D^{22}$ = -215 (c = 0.2, DMSO); IR (KBr) (ν cm^{-1}): 3040, 2984, 1780 (C=O), 1714 (C=O), 1607 (C=N), 1514; ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.89 (d, J = 7.1 Hz, 3H, CH_3), 5.84 (q, J = 7.1 Hz, 1H, N-CH), 7.87-7.94 (m, 6H, aromatic), 8.79 (d, J = 5.0 Hz, 2H, aromatic); ^{13}C-NMR (DMSO-d_6, δ, ppm): δ = 15.4, 47.8, 121.7, 123.5, 132.3, 134.9, 139.8, 150.9, 164.4, 167.8, 168.8; Anal. Calcd. for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49. Found C, 63.58, H, 3.69, N, 17.38.

(*S*)-2-[1-(5-Pyridine-3-yl)-1,3,4-oxadiazole-2-yl) ethyl]isoindoline-1,3-dione (5d):

A) Yield: 53%; B) yield: 35%; mp 147-149 °C; $[\alpha]_D^{22}$ = -180 (c = 0.2, $CHCl_3$); IR (KBr) (ν cm^{-1}): 3037, 2985, 17780 (C=O), 1712 (C=O), 1600 (C=N), 1527; ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.05 (d, J = 7.2 Hz, 3H, CH_3), 5.79 (q, J = 7.1 Hz, 1H, N-CH), 7.59 (d, d, J = 7.2, 4.2 Hz, 1H, aromatic), 7.78-7.82 (m, 2H, aromatic), 7.88-7.92 (m, 2H, aromatic), 8.49 (d, J = 7.9 Hz, 1H, aromatic), 8.80 (s, 1H, aromatic), 9.23 (s, 1H, aromatic); ^{13}C-NMR ($CDCl_3$, δ, ppm): 16.2, 41.7, 120.3, 123.7, 123.9, 131.6, 134.5 (2C), 147.5, 152.1, 163.1, 165.1, 166.8; Anal. Calcd. for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49. Found C, 63.62, H, 3.76, N, 17.41.

(*S*)-2-[2-Phenyl-1-(5-pyridine-4-yl)-1,3,4-oxadiazole-2-yl)ethyl]isoindoline-1,3-dione (5e):

A) Yield: 58%; B) yield: 37%; mp 156-157 °C; $[\alpha]_D^{22}$ = -320 (c = 0.2, DMSO); IR (KBr) (ν cm^{-1}): 3053, 2924, 1772 (C=O), 1720 (C=O), 1608 (C=N), 1554, 1467 (C=C); ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.71-3.80 (m, 2H, CH_2), 6.05 (d, d, J = 10.3, 5.5 Hz, 1H, N-CH), 7.19-7.25 (m, 5H, aromatic), 7.85 (s, 4H, aromatic), 7.92 (d, J = 4.0 Hz, 2H, aromatic), 8.80 (d, J = 3.6 Hz, 2H, aromatic); ^{13}C-NMR (DMSO-d_6, δ, ppm): 34.8, 47.2, 120.7, 124.0, 127.5, 128.9, 129.5, 130.6, 131.1, 135.5, 136.4, 151.5, 163.5, 165.3, 167.2; Anal. Calcd. for $C_{23}H_{16}N_4O_3$: C, 69.69; H, 4.07; N, 14.13. Found C, 69.44, H, 3.95, N, 14.05.

(*S*)-2-[2-Phenyl-1-(5-pyridine-3-yl)-1,3,4-oxadiazole-2-yl)ethyl]isoindoline-1,3-dione (5f):

A) Yield: 54%; B) yield: 34%; mp 157-160 °C; $[\alpha]_D^{22}$ = -172 (c = 0.2, $CHCl_3$); IR (KBr) (ν cm^{-1}): 3044, 2932, 1776 (C=O), 1720 (C=O), 1601 (C=N), 1550, 1456 (C=C), ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.73-3.89 (m, 2H, CH_2), 5.95 (d, d, J = 10.3, 5.5 Hz, 1H, N-CH), 7.12-7.27 (m, 5H, aromatic), 7.50 (d, d, J = 7.5, 4.9 Hz, 1H, aromatic), 7.72-7.85 (m, 4H, aromatic), 8.38 (d, J = 7.9 Hz, 1H, aromatic), 8.79 (s, 1H, aromatic), 9.22 (s, 1H, aromatic); ^{13}C-NMR ($CDCl_3$, δ, ppm): 35.6, 47.3, 120.1, 123.7 (2C), 127.3, 128.7, 129.1, 131.3, 134.3,

134.5, 135.5, 147.9, 152.5, 163.2, 164.2, 167.0; Anal. Calcd. for $C_{23}H_{16}N_4O_3$: C, 69.69; H, 4.07; N, 14.13. Found: C, 69.50, H, 4.04, N, 14.07.

(*S*)-2-[2-Methyl-1-(5-Pyridine-4-yl)-1,3,4-oxadiazole-2-yl)propyl]isoindoline-1,3-dione (5g):

A) Yield: 58%; B) yield: 37%; mp 171-174 °C; $[\alpha]_D^{22}$ = -170 (c = 0.2, $CHCl_3$); IR (KBr) (ν cm^{-1}): 3066, 2960, 1778 (C=O), 1712 (C=O), 1605 (C=N), 1550, 1458 (C=C); ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.00 (d, J = 6.5 Hz, 3H, CH_3), 1.22 (d, J = 6.5 Hz, 3H, CH_3), 2.30-2.36 (m, 1H, CH), 5.13 (d, J = 8.8 Hz, 1H, N-CH), 7.86-7.94 (m, 6H, aromatic), 8.80 (d, J = 3.9 Hz, 2H, aromatic); ^{13}C-NMR ($CDCl_3$, δ, ppm): 19.4, 20.1, 28.5, 44.4, 120.5, 124.1, 130.6, 131.6, 135.5, 152.1, 163.3, 164.0, 167.3; Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.38, H, 4.61, N, 16.01.

(*S*)-2-[2-Methyl-1-(5-Pyridine-3-yl)-1,3,4-oxadiazole-2-yl)propyel]isoindoline-1,3-dione (5h):

A) Yield: 54%; B) yield: 34%; mp 164-166 °C; $[\alpha]_D^{22}$ = -145 (c = 0.2, $CHCl_3$); IR (KBr) (ν cm^{-1}): 3070, 2974, 1772 (C=O), 1718 (C=O), 1608 (C=N), 1550, 1437; ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.04 (d, J = 6.5 Hz, 1H, CH_3), 1.28 (d, J = 6.6 Hz, 1H, CH_3), 2.86-2.89 (m, 1H, CH), 5.34 -5.37 (d, J = 9.0 Hz, 1H, N-CH), 7.55 (d, d, J = 7.5, 4.7 Hz, 1H, aromatic), 7.72-7.87 (m, 4H, aromatic), 8.48 (d, J = 7.8 Hz, 1H, aromatic), 8.77 (s, 1H, aromatic), 9.23 (s, 1H, aromatic); ^{13}C-NMR ($CDCl_3$, δ, ppm): δ = 19.7, 20.5, 29.5, 45.0, 120.3, 123.9 (2C), 131.8, 134.5, 135.1, 147.5, 152.1, 163.2, 164.1, 167.6; Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.27, H, 4.59, N, 15.99.

(*S*)-2-[3-Methyl-1-(5-(pyridine-4-yl)-1,3,4-oxadiazole-2-yl)butyl]isoindoline-1,3-dione (5i):

A) Yield: 50%; B) yield: 30%; mp 144-146 °C; $[\alpha]_D^{22}$ = -177 (c = 0.2, $CHCl_3$); IR (KBr) (ν cm^{-1}): 3078, 2972 1770 (C=O), 1710 (C=O), 1606 (C=N), 1557, 1445; ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.02 (d, J = 6.8 Hz, 3H, CH_3), 1.07 (d, J = 6.8 Hz, 3H, CH_3), 1.48 (m, 1H, CH), 2.10-2.14 (m, 1H, CH_2), 2.51-2.54 (m, 1H, CH_2), 5.79 (d, d, J = 10.5, 5.5 Hz, 1H, N-CH), 7.88-7.95 (m, 6H, aromatic), 8.81 (d, J = 5.1 Hz, 2H, aromatic); ^{13}C-NMR ($CDCl_3$, δ, ppm): 21.5, 22.6, 25.1, 39.0, 47.1, 120.7, 124.5, 130.8, 131.7, 135.3, 151.1, 163.2, 163.5, 167.1; Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N; 15.46. Found: C, 66.11, H, 4.97, N, 15.39.

(*S*)-2-[3-Methyl-1-(5-(pyridine-4-yl)-1,3,4-oxadiazole-2-yl)butyl] isoindoline-1,3-dione (5j):

A) Yield: 51%; B) yield: 30%; mp 140-142 °C; $[\alpha]_D^{22}$ = -127 (c = 0.2, $CHCl_3$); IR (KBr) (ν cm^{-1}): 3070, 2964 1776 (C=O), 1718 (C=O), 1605 (C=N), 1550, 1437; ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.07 (d, J = 6.9 Hz, 3H, CH_3), 1.03 (d, J = 7.0 Hz, 3H, CH_3), 1.50 (m, 1H, CH), 2.11-2.16 (m, 1H, CH_2), 2.53-2.56 (m, 1H, CH_2),

5.80 (d, d, J = 10.6, 5.7 Hz, 1H, N-CH), 7.57-7.61 (m, 1H, aromatic), 7.75-7.89 (m, 4H, aromatic), 8.40 (d, J = 7.6 Hz, 1H, aromatic), 8.87 (s, 1H, aromatic), 9.20 (s, 1H, aromatic); ^{13}C-NMR ($CDCl_3$, δ, ppm): 21.7, 22.8, 25.7, 40.5, 47.6, 120.7, 124.0 (2C), 131.6, 134.1, 135.0 147.8, 152.5, 163.4, 164.3, 167.0; Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.19, H 4.98, N 15.41.

Results and Discussion

Two strategies were used for the synthesis of 1,3,4-oxadiazole compounds **5a-j**. In the first strategy, 1,3,4-oxadiazoles were synthesized through a three-step pathway. N-phetaloyl-L-amino acids **1a-e** (Gly, Ala, Phe, Val, Leu) were synthesized according to the literature.[16] Compounds **1a-e** were converted to the corresponding acyl chlorides **2a-e**,[17] using $SOCl_2$ activation. The reaction of acyl chlorides **2a-e** and pyridoyl hydrazide **3a-b** in N,N-dimethyl acetamide (DMAc) for 3-4 h at room temperature afforded the corresponding semicarbazides **4a-j** in reasonable yields. Then diacyl hydrazides **4a-j** were cyclized to 2,5-disubstituted 1,3,4-oxadiazoles **5a-j** as shown in Figure 1.

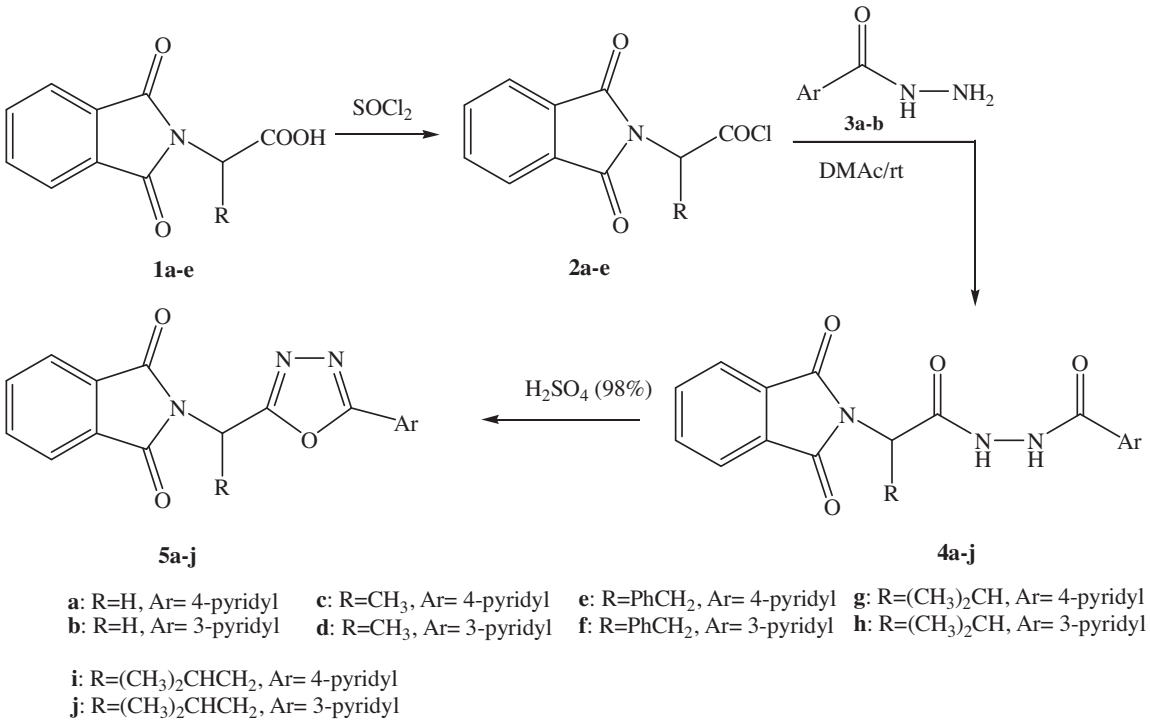
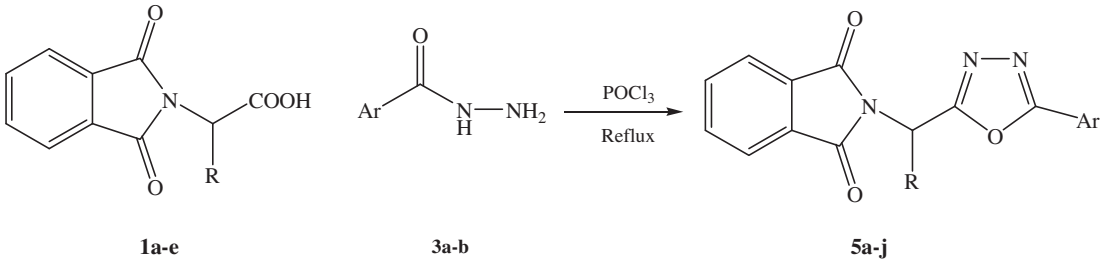


Figure 1. Synthesis of diacyl hydrazides **4a-j** and 1,3,4-oxadiazoles **5a-j**.

Conversion of N-phetaloyl-L-amino acids (especially Val and Leu) to acyl chlorides and purification of acyl chlorides are not simple. We then applied the second strategy as outlined in Figure 2. In this strategy, phosphorus oxychloride was chosen as an anhydrous reagent. The mixture of the N-phetaloyl-L-amino acid **1a-e** (Gly, Ala, Phe, Val, and Leu) and aroryl hydrazides **3a-b** in the presence of $POCl_3$ was refluxed for 36 h. Then the reaction mixture was slowly added to crushed ice with stirring and neutralized with solid potassium carbonate. This procedure offers several advantages such as ease of workup and one pot synthesis.



1a-e **3a-b** **5a-j**

5a: R=H, Ar= 4-pyridyl
5b: R=H, Ar= 3-pyridyl
5c: R=CH_3, Ar= 4-pyridyl
5d: R=CH_3, Ar= 3-pyridyl
5e: R=$PhCH_2$, Ar= 4-pyridyl
5f: R=$PhCH_2$, Ar= 3-pyridyl
5g: R=$(CH_3)_2CH$, Ar= 4-pyridyl
5h: R=$(CH_3)_2CH$, Ar= 3-pyridyl
5i: R=$(CH_3)_2CHCH_2$, Ar= 4-pyridyl
5j: R=$(CH_3)_2CHCH_2$, Ar= 3-pyridyl

Figure 2. Synthesis of 1,3,4-oxadiazoles **5a-j**.

The structure of the synthesized compounds was determined on the basis of spectral data analysis; such as IR, ^{1}H-NMR, and ^{13}C-NMR. For example, the IR spectrum of diacyl hydrazide **4a** showed an absorption bond at 3246 cm^{-1} due to the NH group, which was absent in the IR spectrum of the oxadiazole **5a**. Moreover, the ^{1}H-NMR spectrum of **4a** showed 2 characteristic absorptions (singlet at δ = 10.81 ppm and δ = 10.53 ppm), attributed to the 2 NH groups, which disappeared with the formation of the oxadiazole **5a**.

Conclusion

We synthesized some N-phetaloyl-L-amino acylchlorides having a free terminal carboxyl function, which can react with pyridoyl hydrazides at room temperature to give the intermediates **4a-j**. Then these intermediates are cyclized to **5a-j** at room temperature. This reaction may be useful for combinational synthesis of type **5** compounds having various R and Ar′ substituents with a view to test for biological activities.

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