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\textsubscript{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,\textsuperscript{1} antimitotic,\textsuperscript{2} anti-inflammatory,\textsuperscript{3} anticonvulsant,\textsuperscript{4} and antihepatitis B\textsuperscript{5} activities. In addition to their utility as bioactive molecules, 1,3,4-oxadiazoles are useful intermediates for organic synthesis.\textsuperscript{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,\textsuperscript{7} phosphorus pentoxide,\textsuperscript{8} polyphosphoric acid,\textsuperscript{9} and sulfuric acid.\textsuperscript{10} More recently, however, several methods have been developed using

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A simple and efficient procedure for synthesis of..., N. FOROUGHIFAR, et al.,

essentially neutral conditions and cyclization mediators such as Tf$_2$O$^{11}$ 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-phthaloyl-L-amino acyl chloride 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 distilled 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) ($\nu$, cm$^{-1}$): 3246 (NH), 3041, 2928, 1778 (C=O), 1722 (C=O), 1687 (C=O), 1552, 1421; $^1$H-NMR (DMSO-$d_6$, $\delta$, 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) ($\nu$, cm$^{-1}$): 3196 (NH), 3039, 2939, 1772 (C=O), 1724 (C=O), 1677 (C=O), 1500, 1415; $^1$H-NMR (DMSO-$d_6$, $\delta$, 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) ($\nu$ cm$^{-1}$): 3202 (NH), 3051, 2943, 1776 (C=O), 1712 (C=O), 1664 (C=O), 1552, 1477; $^1$H-NMR (DMSO-$d_6$, $\delta$, ppm): 1.54 (d, $J$ = 7.3 Hz, 3H, 604
A simple and efficient procedure for synthesis of..., N. FOROUGHIFAR, et al.,

CH₃), 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-Dioxoisooindolin-2-yl) propanoyl) nicotinohydrazide (4d):
Yield: 63%; mp 181-183 °C; [α]D² = -110 (c = 0.2, DMSO); IR (KBr) (ν cm⁻¹): 3286 (NH), 2972, 1766 (C=O), 1718 (C=O), 1672 (C=O), 1525; ¹H-NMR (DMSO-d₆, δ, ppm): 1.51 (d, J = 7.1 Hz, 3H, CH₃), 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-Dioxoisooindolin-2-yl)-3-phenyl propanoyl) isonicotinohydrazide (4e):
Yield: 51%; mp 167-170 °C; [α]D² = -235 (c = 0.2, DMSO); IR (KBr) (ν cm⁻¹): 3257 (NH), 3028, 1776 (C=O), 1712 (C=O), 1687 (C=O), 1498, 1421; ¹H-NMR (DMSO-d₆, δ, ppm): 3.54-3.65 (m, 2H, CH₂), 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-Dioxoisooindolin-2-yl)-3-phenyl propanoyl) nicotinohydrazide (4f):
Yield: 58%; mp 176-179 °C; [α]D² = -103 (c = 0.2, DMSO); IR (KBr) (ν cm⁻¹): 3202 (NH), 3051, 2943, 1776 (C=O), 1712 (C=O), 1672 (C=O), 1552 (C=C), 1477; ¹H-NMR (CDCl₃, δ, ppm): 0.81 (d, J = 6.5 Hz, 3H, CH₃), 1.13 (d, J = 6.6 Hz, 3H, CH₃), 2.80-2.85 (m, 1H, CH), 4.56 (d, J = 9.0 Hz, 1H, N-CH), 7.16 (s, 5H, aromatic), 7.52-7.55 (m, 2H, aromatic), 7.81 (b, 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-Dioxoisooindolin-2-yl)-3-methyl butanoyl) isonicotinohydrazide (4g):
Yield: 50%; mp 207-209 °C; [α]D² = -86 (c = 0.2, CDCl₃); IR (KBr) (ν cm⁻¹): 3280 (NH), 2982, 1760 (C=O), 1712 (C=O), 1670 (C=O), 1530, 1450 (C=C); ¹H-NMR (CDCl₃, δ, ppm): 0.84 (d, J = 6.6 Hz, 3H, CH₃), 1.13 (d, J = 6.7 Hz, 3H, CH₃), 2.82-2.89 (m, 1H, CH), 4.47 (d, J = 9.3 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-Dioxoisooindolin-2-yl)-3-methyl butanoyl) nicotinohydrazide (4h):
Yield: 50%; mp 201-203 °C; [α]D² = -70 (c = 0.2, CDCl₃); IR (KBr) (ν cm⁻¹): 3286 (NH), 2972, 1766 (C=O), 1718 (C=O), 1672 (C=O), 1525, 1450 (C=C); ¹H-NMR (CDCl₃, δ, ppm): 0.84 (d, J = 6.6 Hz, 3H, CH₃), 1.13 (d, J = 6.7, 3H, CH₃), 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).
A simple and efficient procedure for synthesis of..., N. FOROUGHIFAR, et al.,

N'- (2-(1,3-Dioxoisooindolin-2-yl)-4-methyl pentanoyl) isonicotinohydrazide (4i):

Yield: 51%; mp 186-187 °C; $[\alpha]_{D}^{22}$ = -115 (c = 0.2, CDCl$_3$); IR (KBr) ($\nu$ cm$^{-1}$); 3277 (NH), 2980, 1760 (C=O), 1712 (C=O), 1670 (C=O), 1530, 1450 (C=C); $^1$H-NMR (CDCl$_3$, $\delta$, 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, 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-Dioxoisooindolin-2-yl)-4-methyl pentanoyl) nicotinohydrazide (4j):

Yield: 50%; mp 179-181 °C; $[\alpha]_{D}^{22}$ = -65 (c = 0.2, CDCl$_3$); IR (KBr) ($\nu$ cm$^{-1}$); 3270 (NH), 2985, 1770 (C=O), 1720 (C=O), 1672 (C=O), 1535, 1427 (C=C); $^1$H-NMR (CDCl$_3$, $\delta$, 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$_2$SO$_4$ (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$_2$O 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) ($\nu$ cm$^{-1}$): 3041, 2928, 1772 (C=O), 1722 (C=O), 1605 (C=N), 1535, 1420 (C=C); $^1$H-NMR (DMSO-d$_6$, $\delta$, 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$_6$, $\delta$, 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$_4$O$_3$: 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) ($\nu$ cm$^{-1}$): 3043, 2933, 1770 (C=O), 1724 (C=O), 1602 (C=N), 1552, 1465 (C=C); $^1$H-NMR (DMSO-d$_6$, $\delta$, ppm): 5.17 (s, 2H, N-CH$_2$), 7.60-7.65 (m, 1H,
A simple and efficient procedure for synthesis of..., N. FOROUGHIFAR, et al.,

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); 13C-NMR (DMSO-d$_6$, $\delta$, 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$_4$O$_3$: 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 $^\circ$C; $[\alpha]_{D}^{22}$ = -215 (c = 0.2, DMSO); IR (KBr) ($\nu$ cm$^{-1}$): 3040, 2984, 1780 (C=O), 1714 (C=O), 1607 (C=N), 1514; 1H-NMR (DMSO-d$_6$, $\delta$, 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); 13C-NMR (DMSO-d$_6$, $\delta$, ppm): $\delta$ = 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$_4$O$_3$: C, 63.75; H, 3.78; N, 17.49. Found C, 63.58, H, 3.69, N, 17.38.

(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 $^\circ$C; $[\alpha]_{D}^{22}$ = -215 (c = 0.2, CHCl$_3$); IR (KBr) ($\nu$ cm$^{-1}$): 3053, 2924, 1772 (C=O), 1720 (C=O), 1608 (C=N), 1554, 1467 (C=C); 1H-NMR (CDCl$_3$, $\delta$, 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), 7.78-7.82 (m, 2H, aromatic), 7.92 (d, J = 4.0 Hz, 2H, aromatic), 8.49 (d, J = 7.9 Hz, 1H, aromatic), 8.80 (s, 1H, aromatic), 9.23 (s, 1H, aromatic); 13C-NMR (CDCl$_3$, $\delta$, ppm): 34.8, 47.2, 120.7, 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$_4$O$_3$: 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 $^\circ$C; $[\alpha]_{D}^{22}$ = -172 (c = 0.2, CHCl$_3$); IR (KBr) ($\nu$ cm$^{-1}$): 3044, 2932, 1776 (C=O), 1720 (C=O), 1601 (C=N), 1550, 1456 (C=C); 1H-NMR (CDCl$_3$, $\delta$, ppm): 3.73-3.89 (m, 2H, aromatic), 5.95 (d, d, $J$ = 10.3, 5.5 Hz, 1H, N-CH), 7.12-7.27 (m, 5H, aromatic), 7.72-7.85 (m, 2H, aromatic), 8.38 (d, J = 7.9 Hz, 1H, aromatic), 8.79 (s, 1H, aromatic), 9.22 (s, 1H, aromatic); 13C-NMR (CDCl$_3$, $\delta$, 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, 164.2, 167.0; Anal. Calcd. for C_{23}H_{16}N_{4}O_{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; [α]_{D}^{22} = -170 (c = 0.2, CHCl_{3}); IR (KBr) (ν cm⁻¹): 3066, 2960, 1712 (C=O), 1510, 1458 (C=C); ^1H-NMR (CDCl_{3}, δ ppm): 1.00 (d, J = 6.5 Hz, 3H, CH₃), 1.22 (d, J = 6.5 Hz, 3H, CH₃), 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); ^13C-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_{4}O_{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]propyl]isoindoline-1,3-dione (5h):
A) Yield: 54%; B) yield: 34%; mp 164-166 °C; [α]_{D}^{22} = -145 (c = 0.2, CHCl_{3}); IR (KBr) (ν cm⁻¹): 3070, 2974, 1772 (C=O), 1718 (C=O), 1550, 1437; ^1H-NMR (CDCl_{3}, δ ppm): 1.04 (d, J = 6.5 Hz, 3H, CH₃), 1.28 (d, J = 6.6 Hz, 1H, CH), 2.86-2.89 (m, 1H, CH), 5.34-5.37 (d, J = 9.0 Hz, 1H, N-CH), 7.55 (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); ^13C-NMR (CDCl_{3}, δ ppm): 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_{4}O_{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; [α]_{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; ^1H-NMR (CDCl_{3}, δ ppm): 1.02 (d, J = 6.8 Hz, 3H, CH₃), 1.07 (d, J = 6.8 Hz, 3H, CH₃), 1.48 (m, 1H, CH), 2.10-2.14 (m, 1H, CH₂), 2.51-2.54 (m, 1H, CH₂), 5.79 (d, J = 10.5, 5.5 Hz, 1H, N-CH), 7.88-7.95 (m, 4H, aromatic), 8.81 (d, J = 5.1 Hz, 2H, aromatic); ^13C-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_{4}O_{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; [α]_{D}^{22} = -127 (c = 0.2, CHCl_{3}); IR (KBr) (ν cm⁻¹): 3078, 2964, 1776 (C=O), 1718 (C=O), 1605 (C=N), 1550, 1437; ^1H-NMR (CDCl_{3}, δ ppm): 1.07 (d, J = 6.9 Hz, 3H, CH₃), 1.03 (d, J = 7.0 Hz, 3H, CH₃), 1.50 (m, 1H, CH), 2.11-2.16 (m, 1H, CH₂), 2.53-2.56 (m, 1H, CH₂), 608
A simple and efficient procedure for synthesis of..., N. FOROUGHIFAR, et al.,

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$_3$, $\delta$, 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$_4$O$_3$: 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. Compounds 1a-e were converted to the corresponding acyl chlorides 2a-e, 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.

![Conversion of N-phetaloyl-L-amino acids 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.]

Figure 1. Synthesis of diacyl hydrazides 4a-j and 1,3,4-oxadiazoles 5a-j.
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![Chemical structures and synthesis reaction](image)

**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 $\delta = 10.81$ ppm and $\delta = 10.53$ 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.

**References**

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