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Research Article

A Straightforward and High-Yielding Synthesis of 1,2,4-Oxadiazoles from Chiral *N*-Protected *α*-Amino Acids and Amidoximes in Acetone-Water: An Eco-Friendly Approach

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A straightforward and high-yielding methodology for the synthesis of a high structural diversity of 1,2,4-oxadiazoles from different chiral *N*-protected *α*-amino acids and amidoximes under microwave (MW) irradiation is described herein. This greener approach gives the desired products using acetone/water as solvent in very short reaction times.

1. Introduction

Among the various classes of heterocyclic compounds, 1,2,4-oxadiazoles are noteworthy due to their usefulness in several applications, including industrial materials, products for agriculture (such as insecticides), and pharmaceutical and medicinal products, representing the largest applicability for these compounds [1–5]. The 1,2,4-oxadiazole nucleus is found in various synthetic drugs displaying a broad biological spectrum of activities, including anti-inflammatory [6, 7], antifungal [8, 9], antibiotic [10, 11], antioxidant [12–14], anticonvulsant [15, 16], and anticancer [17, 18] properties.

Accordingly, several approaches are described in the literature for the preparation of this class of compounds. Generally, the synthesis of 1,2,4-oxadiazoles involves coupling of an amidoxime with an activated carboxyl group, yielding an *O*-acyl amidoxime followed by its dehydrative cyclization. The cyclization of *O*-acyl amidoximes has been carried out by the use of additives such as *N,N′*-dicyclohexylcarbodiimide (DCC) [19, 20], *N*-[3-(dimethylamino) propyl]-*N′*-ethylcarbodiimide (EDC) [21, 22], *N,N′*-carbonyldiimidazole (CDI) [23, 24], *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU) [25, 26], and *N,N′*-diisopropylcarbodiimide (DIC)/HOBt [27, 28].

Despite the diverse number of processes allowing the preparation of the desired 1,2,4-oxadiazoles, there are some drawbacks such as the use of high temperature, long reaction times, and the use of hazardous solvents such as DMF, diglyme, and 1,4-dioxane [19–21, 23, 24, 27].

In recent years, the use of water as a solvent has gained increasing attention in the field of organic synthesis. Water has many advantages over conventional organic solvents, mainly due to its low cost and its nontoxic, nonpolluting, and nonflammable characteristics [29, 30]. On the contrary, the use of microwave mediating organic transformations has arisen as a very useful and effective tool for synthetic protocols due to the strict reaction control, high reaction rates, and energy savings [31, 32]. The use of water as the solvent in microwave transformations has been described. Several reports have shown that, at higher temperature and pressure, water behaves as a pseudoorganic solvent, as the dielectric constant decreases substantially and an ionic product increases the solvating

power towards organic molecules to be similar to that of acetone or ethanol [33–35].

Searching for an alternative protocol for the synthesis of 1,2,4-oxadiazoles, we decided to perform the preparation of these compounds under microwave irradiation, which from a "green" point of view associated with solvent-free conditions represents an environmentally benign alternative in organic synthesis [34, 36, 37].

As part of our growing interest in using α-amino acids as chiral building blocks in organic synthesis [21, 38–45] and in connection with the increasing importance of the synthesis of small libraries of compounds with programmed variations of substituents, we describe herein an assay, an inexpensive synthetic route for the preparation of a set of chiral *N*-protected α-amino acids-derived 1,2,4-oxadiazoles under microwave irradiation, as depicted in Scheme 1.

2. Experimental

2.1. General Information. All commercially available reagents and solvents were used without further purification unless otherwise stated. The experiments were performed in MW Discover CEM using mode of operation with simultaneous cooling. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) or 400 MHz (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz), using a Bruker Avance III HD-400 MHz or a Bruker Avance DPX-200 MHz spectrometers. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts (δ) are reported in parts per million, referenced to TMS. Samples were diluted in 1 : 1 (v/v) acetonitrile: water mixture, containing 0.1% of formic acid. Analyses were performed by infusion mode in an ACQUITY UPLC system from Waters Corp. (Milford, MA, USA) equipped with sampler manager and quadrupole time-of-flight (Q-Tof) MS detector. The Q-Tof Xevo G2 mass spectrometer was equipped with an electrospray ionization source (ESI). Detections were performed in positive ion mode (ESI^+) and resolution mode. Optimized MS conditions were capillary voltage 2.50 kV, cone voltage 15 V, extractor cone 3.30 V, desolvation gas 300 L/h, cone gas 10 L/h, desolvation temperature 300°C, and source temperature 150°C. The acquisition mass range was monitored from 50 to 1000 Da. System control and data acquisition were performed using MassLynx V 4.1 software. Column chromatography was performed using Merck Silica Gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Merck Silica Gel GF254 (0.25 mm thickness). For visualization, TLC plates were placed under ultraviolet light (254 nm) and then soaked in acidic vanillin, followed by heating. The product yields included in all tables refer to isolated yields.

*2.2. Synthesis of Compounds **a–e**, **1–5**, and **1–5** (**a–e**)*

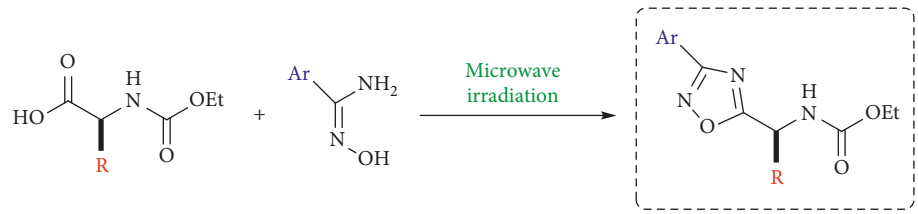
*2.2.1. General Procedure for Preparation of Arylamidoximes **a–e**.* To a stirred solution of appropriate nitrile (**a–e**) (50 mmol) in EtOH (100 mL) was added hydroxylamine hydrochloride (2.2 equiv) and then Et_3N (2.3 equiv). This solution was stirred under reflux for 18 h and then diluted with water. The solvent (EtOH) was removed under reduced pressure, and the aqueous layer extracted 2 times DCM. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by recrystallization using chloroform-heptane or column chromatography over silica gel using a mixture of hexane/EtOAc as the eluent to afford pure aryl amidoximes.

*2.2.2. General Procedure for the Synthesis of Chiral N-Protected Amino Acid-Derived **1–5**.* The *L*-amino acid (10.0 g) was dissolved in H_2O (300 mL), and Na_2CO_3 (2.0 equiv) and $NaHCO_3$ (1.0 equiv) were added at room temperature, with stirring, to give a clear solution. Acetone (4.0 vol.) was added, and the slightly turbid solution was cooled in an ice water bath to 15–20°C. Then, ethyl chloroformate (1.5 equiv) was added slowly, with stirring, and the reaction mixture allowed to warm, to r.t. After stirring for an additional 3 h, the organic layer was concentrated under vacuum. To the aqueous phase was slowly added aqueous HCl, to give a pH of 2. The resulting mixture was extracted into EtOAc (150 mL), and this was washed with H_2O (100 mL) and then concentrated in vacuum to give the *N*-protected amino acid, an oil.

*2.2.3. General Procedure for the Synthesis of 1,2,4-Oxadiazoles (**1–5a–e**) from Chiral N-Protected α-Amino Acids and Amidoximes under Microwave Irradiation.* In a sealed tube in a microwave reactor, 0.8 mmol of *L-N*-protected amino acid (**1–5**) and DCC (0.96 mmol, 0.199 g) were dissolved in acetone (1.0 mL) and the mixture was magnetically stirred for approximately 40 minutes to form the reactive intermediate. Then, 0.8 mmol of aryl amidoxime (**a–e**) was added, and the mixture was homogenized. The acetone was removed in route evaporator without heating, and H_2O (1.0 mL) was added to the mixture, which was subjected to microwave irradiation at 100 W power, temperature of 115°C, during 15 min. Soon after, the reaction crude was dissolved in ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate, 7 : 3) to afford pure products (**1–5a–e**). Detailed experimental procedures, ^{1}H and ^{13}C NMR spectra for all compounds, are available in the supporting information, ESI (available here).

(1) Ethyl((S)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)carbamate (**1a**). White solid; mp: 73-74°C; yield: 76%; $[\alpha]_D^{20} = -18$ (*c* 0.2, CH_2Cl_2), lit. [19] −64 (*c* 0.5, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.06$ (d, $J = 8.1$ Hz, 2H), 7.50–7.40 (m, 3H), 5.58 (br s, 1H), 5.21 (br s, 1H), 4.16 (q, $J = 7.0$ Hz, 2H), 1.64 (d, $J = 7.1$ Hz, 3H), and 1.25 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 179.78$, 168.26, 155.63, 131.19, 128.75, 127.44, 126.54, 61.41, 44.61, 19.91, and 14.43; GCMS (t_R 11.700 min), MS (EI) *m/z* 261 [M^+].

(2) Ethyl((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl) carbamate (**1b**). Yellow solid; mp: 93-94°C; yield: 89%; $[\alpha]_D^{20} = -32$ (c 0.2, CH_2Cl_2), lit. [19] −67 (c 0.6, CH_2Cl_2)];



Scheme 1: Synthesis of 1,2,4-oxadiazoles.

^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.98$ (d, $J = 8.6$ Hz, 2H), 7.43 (d, $J = 8.6$ Hz, 2H,), 5.59 (br s, 1H), 5.21 (br s, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 1.64 (d, $J = 7.2$ Hz, 3H), and 1.25 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 180.03$, 167.45, 155.67, 137.40, 129.11, 128.74, 124.98, 61.47, 44.54, 19.86, and 14.45; GCMS (t_R 12.550 min), MS (EI) m/z 295 [M^+].

(3) Ethyl((S)-1-(3-p-tolyl-1,2,4-oxadiazol-5-yl)ethyl)carbamate (**1c**). White solid; mp: 103–105°C; yield: 83%; $[\alpha]_D^{20} = -24$ (c 0.2, CH_2Cl_2), lit. [19] −13 (c 0.6, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.94$ (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 5.69 (br s, 1H), 5.21 (br s, 1H), 4.15 (q, $J = 7.0$ Hz, 2H,), 2.39 (s, 3H), 1.63 (d, $J = 7.0$ Hz, 3H), and 1.25 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 179.60$, 168.23, 155.69, 141.53, 129.46, 127.36, 123.68, 61.39, 44.57, 21.44, 19.89, and 14.44; GCMS (t_R 12.292 min), MS (EI) m/z 275 [M^+].

(4) Ethyl((S)-1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl) ethyl)carbamate (**1d**). White solid; mp: 121–122°C; yield: 89%; $[\alpha]_D^{20} = -21$ (c 0.2, CH_2Cl_2), lit. [19] −34 (c 0.5, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.98$ (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 5.67 (br s, 1H), 5.18 (br s, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.83 (s, 3H), 1.62 (d, $J = 7.0$ Hz, 3H), and 1.24 (t, $J = 7.2$ Hz, 3H).^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 179.47$, 167.92, 161.96, 155.67, 129.04, 118.94, 114.19, 61.36, 55.27, 44.55, 19.89, and 14.44. GCMS (t_R 13.025 min), MS (EI) m/z 291 [M^+].

(5) Ethyl((S)-1-(3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)ethyl) carbamate (**1e**). Yellow solid; m.p.: 105–106°C; yield: 76%; $[\alpha]_D^{20} = -18$ (c 0.2, CH_2Cl_2), lit. [19] −38 (c 0.7, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.28$ (d, $J = 8.8$ Hz, 2H), 8.21 (d, $J = 9.0$ Hz, 2H), 5.56 (br s, 1H), 5.21 (br s, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 1.66 (d, $J = 7.0$ Hz, 3H), and 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 180.80$, 166.74, 157.74, 155.62, 149.52, 132.39, 128.37, 123.93, 61.50, 44.66, 19.63, and 14.38.

(6) Ethyl((S)-2-phenyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl) carbamate (**2a**). White solid; mp: 96–98°C; yield: 84%; $[\alpha]_D^{20} = -20$ (c 0.2, CH_2Cl_2), lit. [19] +2 (c 0.6, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.08$ (d, $J = 7.6$ Hz, 2H), 7.55–7.40 (m, 3H), 7.33–7.22 (m, 3H), 7.14 (d, $J = 6.6$ Hz, 2H), 5.64 (d, $J = 7.1$ Hz, 1H), 5.47 (br s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.42–3.26 (m, 2H), and 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 178.64$, 168.24, 155.80, 135.07, 131.29, 129.26, 128.82, 128.71, 127.50, 127.32, 126.50, 61.52, 49.80, 39.76, and 14.47.

(7) Ethyl((S)-2-phenyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl) carbamate (**2b**). Yellow solid; mp: 100–101°C; yield: 82%; $[\alpha]_D^{20} = +37$ (c 0.2, CH_2Cl_2), lit. [19] −38 (c 0.55, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.99$ (d, $J = 8.6$ Hz, 2H), 7.44 (d, $J = 8.6$ Hz, 2H), 7.32–7.20 (m, 3H), 7.12 (d, $J = 6.4$ Hz, 2H), 5.61–5.31 (m, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.40–3.22 (m, 2H), and 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 178.84$, 166.44, 155.69, 137.46, 134.90, 129.21, 129.13, 128.79, 128.73, 127.37, 124.98, 61.56, 49.76, 39.76, and 14.43.

(8) Ethyl((S)-1-(3-p-tolyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl) carbamate (**2c**). White solid; mp: 95–97°C; yield: 89%. $[\alpha]_D^{20} = -21$ (c 0.2, CH_2Cl_2), lit. [19] −32 (c 0.65, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.97$ (d, $J = 8.1$ Hz, 2H), 7.32–7.21 (m, 5H), 7.15 (d, $J = 6.4$ Hz, 2H), 5.70 (d, $J = 8.3$ Hz, 1H), 5.46 (br s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.40–3.24 (m, 2H), 2.41 (s, 3H), and 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 178.46$, 168.23, 155.82, 141.61, 135.16, 129.53, 129.28, 128.68, 127.44, 127.28, 123.70, 61.48, 49.80, 39.75, 21.51, and 14.47.

(9) Ethyl((S)-1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-2-phenylethyl)carbamate (**2d**). White solid; mp: 92–94°C; yield: 92%; $[\alpha]_D^{20} = -14$ (c 0.2, CH_2Cl_2), lit. [19] −60 (c 0.7, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.00$ (d, $J = 8.8$ Hz, 2H), 7.32–7.10 (m, 5H), 6.98 (d, $J = 8.8$ Hz, 2H), 5.44 (br s, 2H), 4.14 (q, $J = 7.0$ Hz, 2H), 3.86 (s, 3H), 3.38–3.24 (m, 2H), and 1.24 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 178.21$, 167.92, 162.03, 155.68, 135.01, 129.26, 129.11, 128.68, 127.30, 118.93, 114.23, 61.49, 55.32, 49.73, 39.86, and 14.43.

(10) Ethyl((S)-1-(3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2-phenylethyl)carbamate (**2e**). Yellow solid; mp: 103–105°C; yield: 71%; $[\alpha]_D^{20} = -76$ (c 0.2, CH_2Cl_2), lit. [19] −2 (c 0.5, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.32$ (d, $J = 9.0$ Hz, 2H), 8.24 (d, $J = 8.8$ Hz, 2H), 7.35–7.20 (m, 3H), 7.14 (d, $J = 6.4$ Hz, 2H), 5.44 (br s, 1H), 5.36 (br s, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 3.41–3.28 (m, 2H), and 1.25 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 179.59$, 166.76, 155.52, 149.66, 134.77, 132.35, 129.13, 128.75, 128.43, 127.44, 123.95, 61.59, 49.94, 39.81, and 14.34.

(11) Ethyl((S)-3-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl) carbamate (**3a**). Oil; yield: 81%; $[\alpha]_D^{20} = -30$ (c 0.2, CH_2Cl_2), lit. [19] −46 (c 0.65, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.05$ (d, $J = 7.8$ Hz, 2H), 7.50–7.40 (m, 3H), 5.70 (br s, 1H), 5.19 (br s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 1.85–1.70 (m,

3H), 1.22 (t, $J = 7.1$ Hz, 3H), and 0.95 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 179.84$, 168.21, 156.00, 131.15, 128.72, 127.44, 126.58, 61.36, 47.13, 42.92, 24.57, 22.49, 21.76, and 14.42.

(12) Ethyl((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-3-methylbutyl)carbamate (**3b**). Oil; yield: 80%; $[\alpha]_D^{20} = -28$ (c 0.2, CH_2Cl_2), lit. [19] −41 (c 0.6, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.96$ (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.3$ Hz, 2H), 5.65 (d, $J = 8.8$ Hz, 1H), 5.17 (br s, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 1.80–1.65 (m, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), and 0.95 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 180.04$, 167.40, 155.96, 137.30, 129.04, 128.73, 125.06, 61.41, 47.10, 42.86, 24.57, 22.50, 21.73, and 14.42.

(13) Ethyl((S)-3-methyl-1-(3-p-tolyl-1,2,4-oxadiazol-5-yl)butyl)carbamate (**3c**). Oil; yield: 80%; $[\alpha]_D^{20} = -27$ (c 0.2, CH_2Cl_2), lit. [19] −39 (c 0.7, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.95$ (d, $J = 8.3$ Hz, 2H), 7.26 (d, $J = 8.1$ Hz, 2H), 5.50 (br s, 1H), 5.19 (br s, 1H), 4.16 (q, $J = 6.8$ Hz, 2H), 2.39 (s, 3H), 1.80–1.60 (m, 3H), 1.25 (t, $J = 6.8$ Hz, 3H), and 0.98 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 179.58$, 168.24, 155.91, 141.49, 129.45, 127.39, 123.75, 61.40, 47.12, 43.10, 24.60, 22.51, 21.82, 21.45, and 14.43.

(14) Ethyl((S)-1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-3-methylbutyl)carbamate (**3d**). Oil; yield: 88%; $[\alpha]_D^{20} = -30$ (c 0.2, CH_2Cl_2), lit. [19] −42 (c 0.6, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.95$ (d, $J = 8.3$ Hz, 2H), 6.91 (d, $J = 8.1$ Hz, 2H), 5.76 (br s, 1H), 5.14 (br s, 1H), 4.11 (q, $J = 6.8$ Hz, 2H), 3.78 (s, 3H), 1.80–1.65 (m, 3H), 1.19 (t, $J = 6.8$ Hz, 3H), and 0.93 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 179.47$, 167.88, 161.94, 155.88, 129.00, 119.08, 114.14, 61.26, 55.17, 47.14, 42.92, 24.56, 22.43, 21.73, and 14.36.

(15) Ethyl((S)-3-methyl-1-(3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)butyl)carbamate (**3e**). Oil; yield: 75%; $[\alpha]_D^{20} = -57$ (c 0.2, CH_2Cl_2), lit. [19] −32 (c 0.5, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.28$ (d, $J = 8.8$ Hz, 2H), 8.22 (d, $J = 9.0$ Hz, 2H), 5.51 (d, $J = 8.3$ Hz, 1H), 5.19 (br s, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 1.85–1.69 (m, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), and 0.98 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 180.77$, 166.70, 155.92, 149.44, 132.44, 128.39, 123.95, 61.52, 47.19, 42.78, 24.61, 22.49, 21.71, and 14.40.

(16) Ethyl((R)-2-(benzylthio)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)carbamate (**4a**). White solid; mp: 91–93°C; yield: 60%; $[\alpha]_D^{20} = -12$ (c 0.2, CH_2Cl_2), lit. [19] −25 (c 0.6, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.10$ (d, $J = 8.3$ Hz, 2H), 7.55–7.43 (m, 3H), 7.35–7.22 (m, 5H), 5.72 (br s, 1H), 5.36 (br s, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.70 (s, 2H), 3.05 (d, $J = 5.9$ Hz, 2H), and 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 177.92$, 168.40, 155.75, 137.23, 131.35, 128.92, 128.83, 128.65, 127.53, 127.34, 126.40, 61.69, 48.35, 36.51, 34.82, and 14.47. HRMS-ESI(+) m/z calculated for $C_{20}H_{21}N_3O_3S$ $[(M + Na)^+]$: 406.1201; found: 406.1199.

(17) Ethyl((R)-2-(benzylthio)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl) carbamate (**4b**). White solid; mp: 94–96°C; yield: 55%; $[\alpha]_D^{20} = -48$ (c 0.2, CH_2Cl_2), lit. [19] −29 (c 0.6, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.01$ (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.34–7.23 (m, 5H), 5.75 (br s, 1H), 5.33 (br s, 1H), 4.18 (q, $J = 7.0$ Hz, 2H), 3.69 (s, 2H), 3.03 (d, $J = 5.6$ Hz, 2H), and 1.28 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 178.19$, 167.58, 155.69, 137.52, 137.20, 129.15, 128.88, 128.81, 128.63, 127.35, 124.93, 61.69, 48.41, 36.54, and 34.76, 14.46. HRMS-ESI(+) m/z calculated for $C_{20}H_{20}ClN_3O_3S$ $[(M + Na)^+]$: 440.0812; found: 440.0812.

(18) Ethyl((R)-2-(benzylthio)-1-(3-p-tolyl-1,2,4-oxadiazol-5-yl)ethyl)carbamate (**4c**). White solid; mp: 63–65°C; yield: 60%; $[\alpha]_D^{20} = -65$ (c 0.2, CH_2Cl_2), lit. [19] −34 (c 0.5, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.98$ (d, $J = 8.1$ Hz, 2H), 7.35–7.19 (m, 7H), 5.76 (br s, 1H), 5.35 (br s, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.69 (s, 2H), 3.03 (d, $J = 5.6$ Hz, 2H), 2.42 (s, 3H), and 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 177.73$, 168.40, 155.76, 141.69, 137.26, 129.53, 128.92, 128.62, 127.45, 127.31, 123.58, 61.66, 48.35, 36.49, 34.82, 21.51, and 14.47. HRMS-ESI(+) m/z calculated for $C_{21}H_{23}N_3O_3S$ $[(M + Na)^+]$: 420.1358; found: 420.1345.

(19) Ethyl((R)-2-(benzylthio)-1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl) carbamate (**4d**). White solid; mp: 107–109°C; yield: 70%; $[\alpha]_D^{20} = -10$ (c 0.2, CH_2Cl_2), lit. [19] −22 (c 0.7, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.01$ (d, $J = 8.8$ Hz, 2H), 7.34–7.22 (m, 5H), 6.98 (d, $J = 9.0$ Hz, 2H), 5.76 (br s, 1H), 5.33 (br s, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.85 (s, 3H), 3.68 (s, 2H), 3.02 (d, $J = 5.6$ Hz, 2H), and 1.27 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 177.59$, 168.07, 162.07, 155.75, 137.27, 129.13, 128.91, 128.61, 127.30, 118.83, 114.26, 61.63, 55.33, 48.32, 36.47, 34.80, and 14.47. HRMS-ESI(+) m/z calculated for $C_{21}H_{23}N_3O_4S$ $[(M + Na)^+]$: 436.1307; found: 436.1283.

(20) Ethyl((R)-2-(benzylthio)-1-(3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate (**4e**). Oil; yield: 63%; $[\alpha]_D^{20} = -14$ (c 0.2, CH_2Cl_2), lit. [19] −14 (c 0.4, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.29$ (d, $J = 8.8$ Hz, 2H), 8.23 (d, $J = 8.6$ Hz, 2H), 7.35–7.20 (m, 5H), 5.76 (d, $J = 7.1$ Hz, 1H), 5.33 (br s, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.72 (s, 2H), 3.06 (d, $J = 6.4$ Hz, 2H), and 1.27 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 178.95$, 166.85, 155.68, 149.59, 137.15, 132.24, 128.84, 128.64, 128.45, 127.37, 123.99, 61.75, 48.49, 36.60, 34.67, and 14.43. HRMS-ESI(+) m/z calculated for $C_{21}H_{23}N_3O_4S$ $[(M + Na)^+]$: 451.1052; found: 451.1033.

(21) Ethyl((S)-3-(methylthio)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl)carbamate (**5a**). White solid; mp: 60–62°C; yield: 84%; $[\alpha]_D^{20} = -28$ (c 0.2, CH_2Cl_2), lit. [19] −34 (c 0.65, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.02$ (d, $J = 7.8$ Hz, 2H), 7.45–7.36 (m, 3H), 5.92 (br s, 1H), 5.27 (br s, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.58 (t, $J = 7.2$ Hz, 2H), 2.32–2.17 (m, 2H), 2.06 (s, 3H), and 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 178.87$, 168.23, 155.99, 131.24,

128.76, 127.42, 126.43, 61.50, 47.91, 32.07, 29.74, 15.31, and 14.43.

(22) Ethyl((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-3-(methylthio)propyl) carbamate (**5b**). Oil; yield: 91%; $[\alpha]_D^{20} = -33$ (*c* 0.2, CH_2Cl_2), lit. [19] −44 (*c* 0.55, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.92$ (d, $J = 8.6$ Hz, 2H), 7.37 (d, $J = 8.6$ Hz, 2H), 5.88 (d, $J = 8.6$ Hz, 1H), 5.24 (br s, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 2.58 (t, $J = 7.0$ Hz, 2H), 2.32–2.15 (m, 2H), 2.05 (s, 3H), and 1.19 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 178.94$, 167.24, 155.74, 137.18, 128.87, 128.53, 124.80, 61.35, 47.79, 32.88, 29.61, 15.13, and 14.22.

(23) Ethyl((S)-1-(3-p-tolyl-1,2,4-oxadiazol-5-yl)-3-(methylthio)propyl)carbamate (**5c**). Oil; yield: 88%; $[\alpha]_D^{20} = -29$ (*c* 0.2, CH_2Cl_2), lit. [19] −48 (*c* 0.65, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.89$ (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 7.8$ Hz, 2H), 5.97 (br s, 1H), 5.24 (br s, 1H), 4.12 (q, $J = 7.0$ Hz, 2H), 2.57 (t, $J = 7.0$ Hz, 2H), 2.34 (s, 3H), 2.32–2.11 (m, 2H), 2.05 (s, 3H), and 1.20 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 178.72$, 168.24, 156.04, 141.58, 129.49, 127.38, 123.65, 61.50, 47.93, 33.11, 29.78, 21.45, 15.32, and 14.46.

(24) Ethyl((S)-1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-3-(methylthio)propyl) carbamate (**5d**). mp: 105–106°C; yield: 81%; $[\alpha]_D^{20} = -29$ (*c* 0.2, CH_2Cl_2), lit. [19] −47 (*c* 0.4, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.96$ (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 5.82 (br s, 1H), 5.25 (br s, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 3.81 (s, 3H), 2.59 (t, $J = 7.0$ Hz, 2H), 2.34–2.15 (m, 2H), 2.07 (s, 3H), and 1.22 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 178.45$, 167.95, 162.03, 155.85, 129.04, 118.92, 114.23, 61.49, 55.27, 47.98, 33.27, 29.77, 15.32, and 14.40.

(25) Ethyl((S)-3-(methylthio)-1-(3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate (**5e**). Oil; yield: 70%; $[\alpha]_D^{20} = -32$ (*c* 0.2, CH_2Cl_2), lit. [19] −18 (*c* 0.45, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.26$ (d, $J = 8.8$ Hz, 2H), 8.19 (d, $J = 8.8$ Hz, 2H), 5.87 (d, $J = 8.6$ Hz, 1H), 5.28 (br s, 1H), 4.11 (q, $J = 7.0$ Hz, 2H), 2.61 (t, $J = 7.0$ Hz, 2H), 2.37–2.20 (m, 2H), 2.08 (s, 3H), and 1.21 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 179.88$, 166.74, 155.86, 149.51, 132.31, 128.38, 123.94, 61.62, 48.01, 32.92, 29.79, 15.33, and 14.38.

3. Results and Discussion

The synthetic approach to give the 1,2,4-oxadiazoles was performed, starting from the protected amino acids shown in Figure 1.

The *L*-amino acids alanine (**1**), phenylalanine (**2**), leucine (**3**), *S*-benzyl-*L*-cysteine (**4**), and methionine (**5**) were conveniently protected by treatment with ethyl chloroformate in an aqueous sodium bicarbonate solution [46].

In order to determine the optimal reaction conditions for the synthesis of 1,2,4-oxadiazole derivatives, we carried out the reaction employing the protected amino acid methionine (**5**) and aryl amidoxime (**b**) as a model substrate. In this set of experiments, we studied the effect of the temperature, reaction time, and solvents in order to determine the optimal reaction conditions (Table 1).

As described in Table 1 (Entries **9**–**11**), the use of less polar solvents such as toluene, THF, and 1,4-dioxane are clearly less suitable for microwave-assisted synthesis, because their dielectric constants are substantially lower [37, 46]. The use of a small amount of ionic liquid ($BMIMBF_4$) as a "doping agent" for microwave heating of the nonpolar solvents (THF, 1,4-dioxane, and toluene) allowed heating above boiling points in sealed vessels [37, 47–49], with the formation of the products in moderate to good yields (Table 1, Entries **2**, **4**, and **8**). Since these less polar solvents poorly absorb MW irradiation due to their lower loss tangent, the use of ionic liquid as a doping agent becomes essential to achieve high temperature (160°C).

The best result was obtained using DCC which furnished the desired product in the best yield. As observed in Table 1, the best solvent for this reaction was the mixture acetone/water, affording the respective compound (**5b**) in 91% yield in 15 min (Table 1, Entry **13**). Increasing the reaction temperature from 115 to 160°C resulted in a decrease in yield to 50% (Entry **6**). The influence of coupling agents was also studied in order to determine the most efficient promoter for this transformation. Thus, a series of coupling agents including CDI, DCC, DIC, and TBTU was used to afford the 1,2,4-oxadiazole.

The extensive reduction in the reaction time in the microwave-assisted conditions along with a very simple work-up, better yield as well as the use of acetone/water as solvent when compared with conventional heating [19], makes more benign protocol to the environment in the process synthesis of the compound (**5b**).

With the optimized reaction conditions determined, we extended the protocol to a broader range of protected amino acids (**1–5**) as shown in Figure 1 and to a set of aryl amidoximes (**a–e**), in the presence of DCC, using microwave irradiation (Table 2). The 1,2,4-oxadiazoles were obtained in moderate to good yields (62–92%).

An important point to note is the primary activation of the carboxyl in the amino acid by DCC and the subsequent aryl amidoxime addition in the reaction medium. This sequence of reagents is an important factor, especially because the amidoxime can also react with DCC, before the activation of the carboxyl in the amino acid residue, resulting in undesired byproducts.

The process of formation of the intermediate **I** was carried for approximately 40 minutes, at room temperature, with the use of acetone as the solvent, which is also considered a solvent with green features [50]. The solvent was subsequently removed by evaporation under reduced pressure, without heating. After this, water was added to the formed intermediate I, and then, the reaction mixture was subjected to microwave irradiation (Table 2).

The electronic effect of the substituents at the aryl amidoximes was studied. Amidoximes containing electron-donating groups such as methyl and methoxy and electron-withdrawing groups such as chloro and nitro were prepared (Table 2, compounds **1–5c, d**).

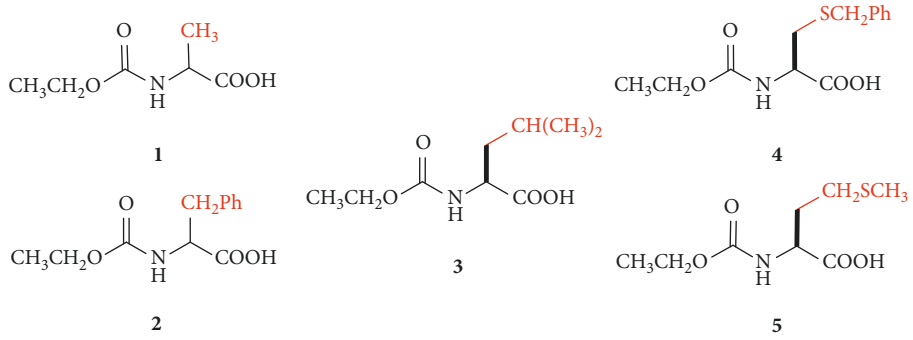
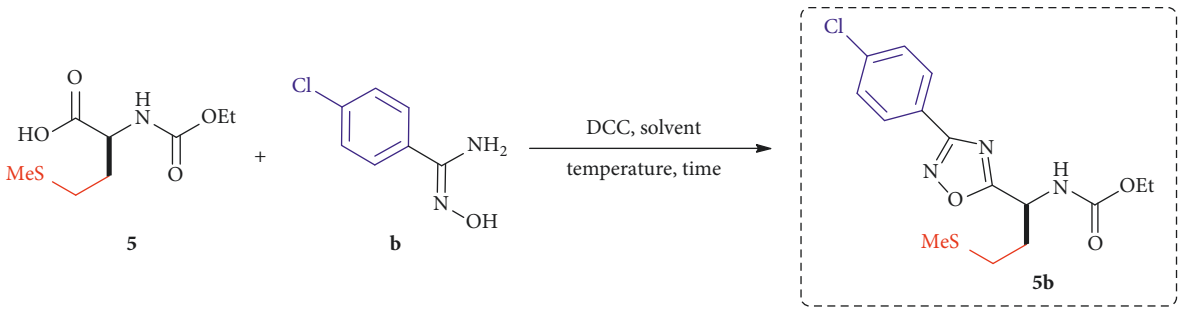


Figure 1: Chiral protected amino acids used for the synthesis of 1,2,4-oxadiazoles. "Figure 1 is reproduced from [45] (under the Creative Commons Attribution License/public domain)".

Table 1: Optimization of the reaction conditions for the synthesis of 1,2,4-oxadiazoles **5b** by microwave irradiation.



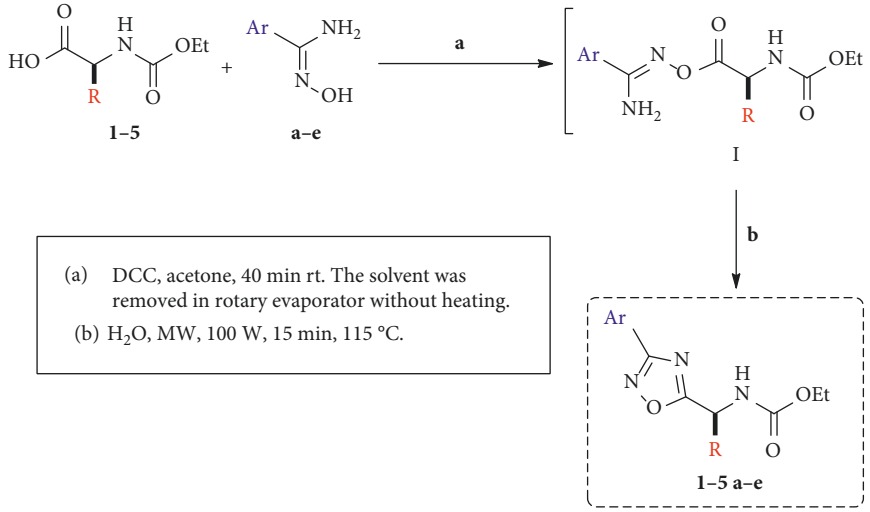
Entry	T (°C)	Solvent	Time (min)	Yield (%)[4]
1	160	—	10	37
2	160	Toluene[1]	10	35
3	160	EtOH[1]	10	61
4	160	THF[1]	10	86
5	160	1,4-Dioxane[1]	10	52
6	160	Acetone/H_2O[2]	10	50
7	115	THF[1]	15	78
8	115	1,4-Dioxane[2]	15	76
9	115	Toluene[3]	15	25
10	115	THF[3]	15	50
11	115	1,4-Dioxane[3]	15	56
12	115	Acetone/H_2O[2]	10	79
13	115	Acetone/H_2O[2]	15	91
14	115	Acetone/H_2O[2]	20	76
15	80	THF[1]	15	42
16	80	1,4-Dioxane[1]	15	52
17	80	Acetone/H_2O[2]	15	77
18	80	Acetone/H_2O[2]	20	80
19	80	Acetone/H_2O[2]	30	61

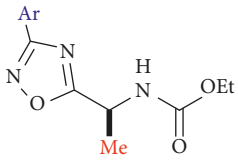
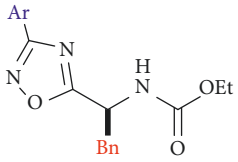
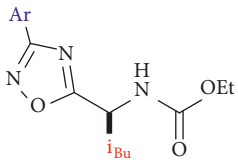
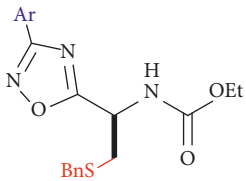
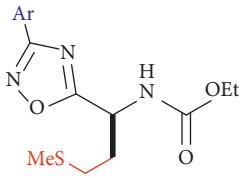
[1]Mixture of 1.0 mL of solvent and 0.5 mL of $BMIMBF_4$. [2]1.0 mL of acetone and 1.0 mL of water as solvent. [3]1.0 mL of solvent. [4]Yields for isolated pure products.

In this way, the presence of strong electron-withdrawing groups such as nitro (NO_2) yield slightly lower products compared with donating or soft electron-withdrawing groups (Table 2, compounds **1–5e** and **1–5a–d**, respectively). This result could be explained by the reduced nucleophilicity in aryl amidoximes when this group is directly attached. Electron-donating and soft withdrawing groups allowed the preparation of the respective 1,2,4-oxadiazoles with similar efficiency.

In terms of amino acids, the nature of the side chain does not play a significant role in terms of conversion to the desired heterocycle, since the results obtained with lipophilic and sulfurated side chains were quite similar. An exception was observed for the derivatives of *S*-benzyl-*L*-cysteine (Table 2, compounds **4a–e**) probably due to the formation of by-products. Despite the small difference in the reactivity of the aryl amidoximes, all the 1,2,4-oxadiazoles were obtained in moderate to good yields for all

Table 2: Synthesis of α-amino acid-derived 1,2,4-oxadiazoles under microwave irradiation.



Compounds	Yield (%) [1,2]
	Ar: Ph **1a** = 76% 4-ClC_6H_4 **1b** = 89% 4-MeC_6H_4 **1c** = 83% 4-$MeOC_6H_4$ **1d** = 89% 4-$NO_2C_6H_4$ **1e** = 76%
	Ar: Ph **2a** = 84% 4-ClC_6H_4 **2b** = 82% 4-MeC_6H_4 **2c** = 89% 4-$MeOC_6H_4$ **2d** = 92% 4-$NO_2C_6H_4$ **2e** = 71%
	Ar: Ph **3a** = 81% 4-ClC_6H_4 **3b** = 80% 4-MeC_6H_4 **3c** = 80% 4-$MeOC_6H_4$ **3d** = 88% 4-$NO_2C_6H_4$ **3e** = 75%
	Ar: Ph **4a** = 65% 4-ClC_6H_4 **4b** = 65% 4-MeC_6H_4 **4c** = 62% 4-$MeOC_6H_4$ **4d** = 70% 4-$NO_2C_6H_4$ **4e** = 63%
	Ar: Ph **5a** = 84% 4-ClC_6H_4 **5b** = 91% 4-MeC_6H_4 **5c** = 88% 4-$MeOC_6H_4$ **5d** = 81% 4-$NO_2C_6H_4$ **5e** = 70%

[1]Reactions performed in the presence of aryl amidoxime (**a–e**) (0.8 mmol), *N*-protected amino acid (**1–5**) (0.8 mmol), 1.2 equiv DCC, acetone and water as solvent (1.0 mL), 115°C, 15 min, MW irradiation (power of 100 W). [2]Yields for isolated pure products.

the amino acids studied, showing the versatility of the methodology.

4. Conclusions

In conclusion, we developed a straightforward, efficient, and greener procedure for the high structural diversity of 1,2,4-oxadiazoles under microwave irradiation using acetone/water as the solvent in very short reaction times. Moreover, the method using microwave irradiation and water as the solvent is more efficient and greener, allowing the synthesis of 1,2,4-oxadiazoles by carrying out all reactions with an easy work-up, in short reaction times and better yields, when compared to conventional heating [19]. Although a limited number of substituents have been presented, this method can be extended to other substrates, since amino acids are inexpensive and easily available starting materials. The reaction conditions proved to be compatible with the carbamate protective group.

Data Availability

The ^{1}H NMR and ^{13}C NMR spectral data used to support the findings of this study are included within the supplementary information file.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Figures S1–S50: ^{1}H NMR and ^{13}C NMR spectra (compounds **1–5a–e**). (*Supplementary Materials*)

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