Synthesis of 1,3,4-oxadiazole derivatives from α-amino acid and acyl hydrazides under thermal heating or microwave irradiation conditions

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DOI: http://dx.doi.org/10.3998/ark.5550190.p009.310

Abstract

A series of new 2,5-disubstituted 1,3,4-oxadiazoles was synthesized under conventional thermal heating and microwave irradiation conditions through the reaction of acyl hydrazides with *N*-protected α-amino acid in presence of a small amount of $POCl_3$. Heterocycles were obtained in moderate to good yields and in relatively short reaction times.

Keywords: Amino acids, acyl hydrazides, 1,3,4-oxadiazoles, heterocycles, microwave

Introduction

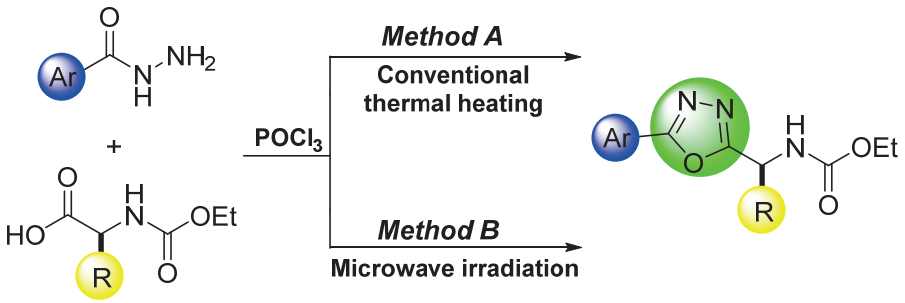
1,3,4-Oxadiazoles and their derivatives constitute an important class of heterocyclic compounds as they have attracted significant interest in medicinal and pesticide chemistry as well as polymer and material science. These derivative compounds have been found to exhibit diverse biological activities such as analgesic,[1,2] anti-inflammatory,[1,2] antimicrobial,[2-4] anti-HIV,[5] antimalarial,[6,7] antifungicidal,[8,9] and other biological properties.[10-14] Some 1,3,4-oxadiazole derivatives have also been applied in the fields of photosensitizers,[15] liquid crystals[16,17] and organic light-emitting diodes (OLED).[18,19] Consequently, the synthesis of compounds containing this heterocyclic core has attracted considerable attention, and a wide variety of methods has been used for their assembly. The most common synthetic protocol toward the preparation of these compounds involves the dehydrative cyclization of diacylhydrazides using usually strong acidic reagents such as thionyl chloride,[20] phosphorus pentoxide,[21] phosphorus oxychloride,[22-25] and sulfuric acid.[26]

In recent years 1,3,4-oxadiazoles have been inserted in route to design new peptidomimetics. These molecules are expected to have the same therapeutic effects as natural peptide counterparts, with the added advantage of metabolic stability. In this context Sureshbabu described the synthesis of 1,3,4-oxadiazole peptidomimetics starting from diacylhydrazines derived from amino acids.[27,28]

On the other hand, amino acids have emerged as important building blocks for the synthesis of a range of different compounds.[29-31] Moreover, the interest on the biological and medicinal properties of chalcogen amino acids has also been increasingly appreciated, mainly due to their antioxidant,[32] antitumor,[33] antimicrobial,[34] and antiviral[35] properties.

Results and Discussion

As part of our growing interest in using α-amino acids as chiral building blocks in organic synthesis,[36-38] and in connection with the increasing importance of the synthesis of small libraries of compounds with programmed variations of substituents, we describe herein an easy and inexpensive one-pot synthetic route for the preparation of a set of chiral *N*-protected chiral α-amino acid derived 1,3,4-oxadiazoles under conventional thermal heating and microwave irradiation, as depicted in the Scheme 1.



Scheme 1. Synthesis of 1,3,4-oxadiazoles.

The synthetic route to afford the 1,3,4-oxadiazoles was applied on appropriately protected amino acids shown in Figure 1. The *L*-amino acids alanine (**1**), phenylalanine (**2**), leucine (**3**), *S*-benzyl-cysteine (**4**) and methionine (**5**) were conveniently protected by the treatment with ethyl chloroformate in an aqueous sodium bicarbonate solution.[36,39] The *N*-protected selenoamino acid **6** was prepared from serine following the procedures already described in the literature.[40]

In order to determine the optimal reaction conditions for the synthesis of 1,3,4-oxadiazole derivatives from protected α-amino acids, we decided to initiate our studies toward the conventional thermal heating protocol (heating with oil bath). To accomplish this transformation, we carried out the reaction employing equimolar protected L-phenylalanine derivative **2** and benzoyl hydrazide **a** as a model reaction. In this set of experiments, a variety of different solvents and dehydrating agents were tested with the objective to determine the best reaction condition (Table 1).

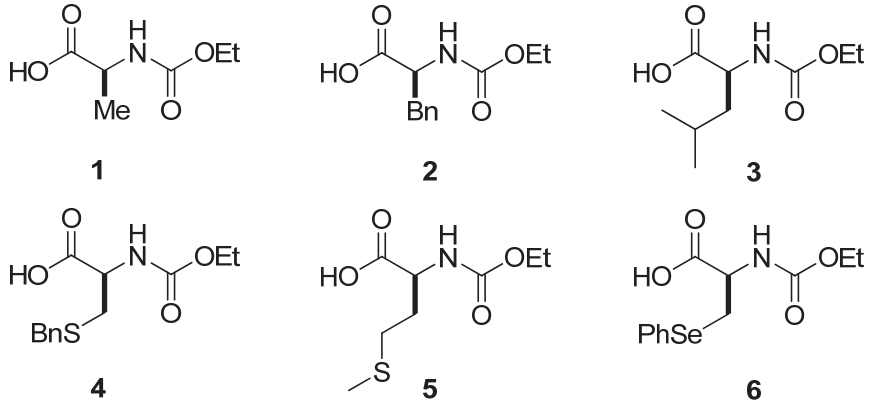
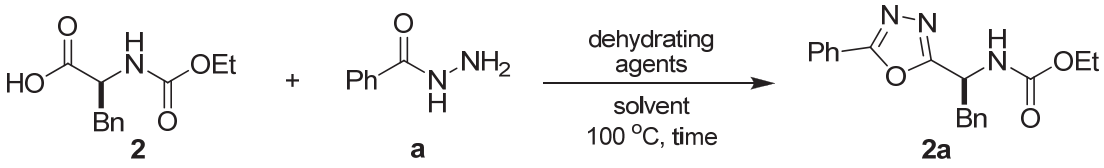


Figure 1. Chiral protected amino acids used as a building block for the synthesis of 1,3,4-oxadiazoles.

Table 1. Optimization of the reaction conditions for the synthesis of 1,3,4-oxadiazoles **2a** by conventional heating.[a]



Entry	Solvent	Dehydrating agent	Time (h)	Yield (%)[b]
1	1,4-dioxane	$POCl_3$	8	63
2	1,4-dioxane	$POCl_3$	24	45
3	THF	$POCl_3$	8	56
4	Toluene	$POCl_3$	8	53
5	$POCl_3$	$POCl_3$	8	traces
6	1,4-dioxane	$SOCl_2$	8	32
7	1,4-dioxane	H_2SO_4	8	0
8	1,4-dioxane	DCC	8	56
9	1,4-dioxane	$BF_3.OEt_2$	8	0
10	neat, microwave	$POCl_3$	4[c]	70

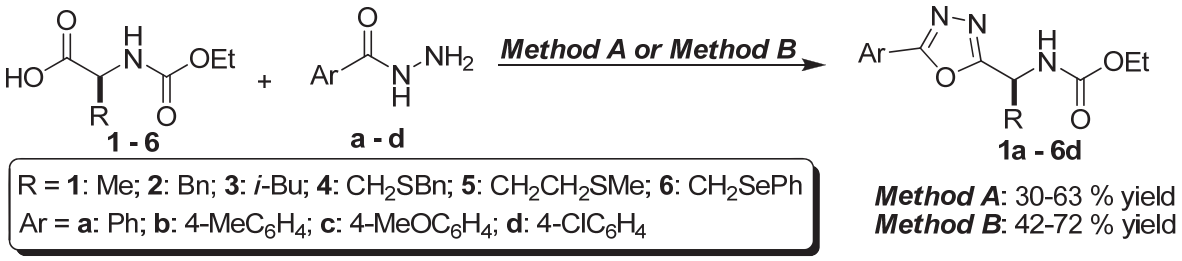
[a] Reactions performed in the presence of protected L-phenylalanine derivative **2** (0.5 mmol), benzoyl hydrazide **a** (0.5 mmol), dehydrating agent (4.3 mmol) and solvent (8.0 mL) under nitrogen atmosphere. [b] Yields for isolated pure products. [c] Time in minutes.

As observed in Table 1, the best solvent for this reaction was 1,4-dioxane, affording the respective compound **2a** in 63% of yield in 8 h (Table 1, Entry 1). When the reaction time was

increased from 8 h to 24 h, a decrease in the yield to 45% was observed (Entry 2). The influence of dehydrating agents was also studied in order to determine the most efficient promoter of this transformation. In this context, a series of dehydrating agents such as $POCl_3$, $SOCl_2$, H_2SO_4, DCC and BF_3.OEt was used to afford the 1,3,4-oxadiazole. Initially, the reaction was conducted with variable amounts of $POCl_3$. The best result was obtained using $POCl_3$ (4.3 mmol for 0.5 mmol of aminoacid), which furnished the desired product in a better yield (Table 1, Entry 1). The increase (6.3 mmol) or decrease (2.1 mmol) of the amount of dehydrating agent led to formation of product with lower yields (56 and 60%, respectively). On the other hand, other dehydrating agents such as $SOCl_2$ and DCC gave only moderate yields (Table 1, Entries 6 and 8). No product formation was observed when H_2SO_4 and BF_3.OEt were used (Entries 7 and 9).

Searching for an alternative protocol for the synthesis of 1,3,4-oxadiazoles, we decided to perform the preparation of these compounds under microwave irradiation. From a "green" point of view, when associated with neat conditions it represents an environmentally-benign alternative in organic synthesis.[41,42] To accomplish this, we used the same molar ratio employed in the conventional heating. From Table 1 (Entry 10), we can observe that microwave irradiation afforded the respective compound **2a** in a slightly better yield - compared with the thermal conventional heating – and in a short reaction time.

With the reaction conditions optimized, we extended the protocol to a broader range of protected amino acids **1-6** as shown in Figure 1 and to a variety of commercial hydrazides in the presence of phosphorus oxychloride using conventional heating protocols and microwave (Scheme 2).



Scheme 2. Synthesis of 1,3,4-oxadiazoles **3.** *Method A*: *N*-protected amino acid **1-6** (0.5 mmol), aryl hydrazide **a-d** (0.5 mmol), $POCl_3$ (4.3 mmol), 1,4-dioxane (8.0 mL), 100°C, 4-8 h. *Method B*: *N*-protected amino acid **1-6** (0.5 mmol), aryl hydrazide **a-d** (0.5 mmol), $POCl_3$ (4.3 mmol), microwave (3-5 min).

The electronic effect of the substituents of the aryl hydrazides was studied. For this purpose, hydrazides containing electron-donating groups such as methyl and methoxy and an electron-withdrawing group such as chloro were prepared (Table 2, Entries 7-24). We could observe that all the 1,3,4-oxadiazoles were obtained in moderate to good yields for all the amino acids studied, showing that the substitution pattern at the aromatic ring of the hydrazide does not exert a strong influence in the heterocycle formation. Regarding 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. For the synthesis of 1,3,4-oxadiazoles using the amino acid derived from *N*-protected selenoamino acid **6**, both methodologies allowed the preparation of the compounds with similar efficiency (Table 2, Entries 6, 12, 18 and 24).

Table 2. Synthesis of 1,3,4-oxadiazoles **1a-6d** under conventional heating and under microwave irradiation

		Conventional method		Microwave method	
Entry	Compounds	Time (h)	Yield (%)	Time (min)	Yield (%)[a]
1	**1a**	7	51	4	62
2	**2a**	8	63	3	70
3	**3a**	7	55	4	67
4	**4a**	8	40	4	54
5	**5a**	7	58	3	63
6	**6a**	8	51[b]	4	52[c]
7	**1b**	8	45	4	63
8	**2b**	8	40	4	72
9	**3b**	8	41	4	60
10	**4b**	8	30	4	55
11	**5b**	8	35	4	64
12	**6b**	8	66[b]	4	54[c]
13	**1c**	7	40	4	57
14	**2c**	8	46	4	70
15	**3c**	8	40	4	62
16	**4c**	8	35	4	53
17	**5c**	8	42	5	60
18	**6c**	8	57[b]	4	52[c]
19	**1d**	8	44	4	50
20	**2d**	8	35	4	62
21	**3d**	8	38	4	42
22	**4d**	8	35	4	52
23	**5d**	8	30	4	43
24	**6d**	8	50[b]	4	47[c]

[a] Yields for isolated pure products. [b] Reaction at 80°C. [c] 1mL of 1,4-dioxane was added.

The results obtained in this study using conventional heating and microwave irradiation were compared. Table 2 shows the results for the synthesis of 1,3,4-oxadiazoles **1a-6d**, using the two different methods. In most of the cases the microwave-assisted conditions were found to be superior and the 1,3,4-oxadiazoles were obtained in moderate to good yields (42-72%).

Conclusions

In conclusion, the two methodologies studied for the synthesis of 1,3,4-oxadiazoles use a small amount of the dehydrating agent $POCl_3$, when compared with other methodologies reported in the literature.[22-25] The dramatically shorter reaction time in the microwave-assisted conditions along with a very simple work-up, better yields as well as the absence of solvent when compared with conventional heating make the protocol more environmentally benign for the synthesis of 1,3,4-oxadiazoles.

Experimental Section

General. The following solvents were dried and purified by distillation from the reagents indicated: THF from sodium with benzophenone indicator, 1,4-dioxane from KOH and toluene under P_2O_5. All other solvents were ACS or HPLC grade unless otherwise noted. Proton magnetic resonance (^{1}H NMR) spectra were obtained on a Bruker DPX - 400 MHz or DPX - 200 MHz spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million, referenced to TMS. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 50 MHz or 100 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Selenium nuclear magnetic resonance (^{77}Se NMR) spectra were recorded on a Bruker DPX 400 MHz, at 76.28 MHz with diphenyl diselenide as the ^{77}Se external reference (463 ppm). Accurate mass measurement was performed on XEVO G2 QTOF-Waters mass spectrometer. Optical rotations were carried out on a Perkin Elmer Polarimeter 341. 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. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapor or acidic vanillin.

General procedure for the synthesis of 1,3,4-oxadiazoles (1a-6d)

Method A. conventional thermal heating: To a 50 mL round-bottomed flask equipped with a reflux condenser, under argon atmosphere, $POCl_3$ (4.3 mmol) was added to a solution of the appropriate *N*-protected amino acid **1-6** (0.5 mmol) and the aryl hydrazide **a-d** (0.5 mmol) in dry 1,4-dioxane (8 mL). The reaction mixture was heated under stirring at 80-100 ^{o}C for the time indicated in **Table 1**. After this time, the mixture was cooled to room temperature and diluted with 30 mL of CH_2Cl_2. The organic phase was washed with 2 M HCl (10 mL), followed by saturated sodium bicarbonate solution and then water. The organic phase was dried over magnesium sulfate and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (hexane-ethyl acetate, 7:3) to afford pure products (**1a-6d**)

Method B. microwave irradiation: To a 5 mL glass tube, $POCl_3$ (4.3 mmol) was added to this mixture of *N*-protected amino acid **1-6** (0.5 mmol) and aryl hydrazide **a-d** (0.5 mmol). For the reactions using *N*-protected selenoamino acid **6** were used 1 mL of 1,4-dioxane to solubilize the

starting materials. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 100 ± 5 ºC, power 200-250 W. The tube was irradiated in the microwave oven for appropriate time and temperature (according to **Table 2**). After completion of the reaction (monitored by TLC using hexane:ethyl acetate, 7:3). The work-up and purification step was the same used for conventional thermal heating.

Ethyl (*S*)-*N*-[1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate(1a). Yield: 51% (Method A) and 62% (Method B). White solid, mp 84 - 86 °C. $[\alpha]_D^{20}$ = -34 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.03 (d, *J* 6.6 Hz, 2H), 7.56-7.46 (m, 3H), 5.49-5.45 (m, 1H), 5.26-5.17 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 1.68 (d, *J* 7.0 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): *δ* 167.03, 165.12, 155.68, 131.80, 129.01, 126.94, 123.68, 61.45, 43.56, 19.76, 14.49. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{13}H_{15}N_3NaO_3$ 284.1011, found 284.1017.

Ethyl (*S*)-*N*-[2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (2a). Yield: 63% (Method A) and 70% (Method B). White solid, mp 87 - 89 °C. $[\alpha]_D^{25}$ = -12 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.07 (s, 1H), 7.89 (d, *J* 7.8 Hz, 1H), 7.66-7.62 (m, 1H), 7.34 (t, *J* 7.9 Hz, 1H), 7.30-7.24 (m, 3H), 7.16 (d, *J* 6.6 Hz, 2H), 5.56 (d, *J* 8.7 Hz, 1H), 5.44-5.37 (m, 1H), 4.12 (q, *J* 7.1 Hz, 2H), 3.32 (d, *J* 6.7 Hz, 2H), 1.22 (t, *J* 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): *δ* 166.31, 163.65, 155.72, 135.31, 134.73, 130.53, 129.71, 129.25, 128.69, 127.29, 125.38, 123.01, 61.51, 48.88, 39.82, 14.42. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{19}H_{19}N_3NaO_3$ 360.1324, found 360.1325.

Ethyl (*S*)-*N*-[3-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)butyl]carbamate (3a). Yield: 55% (Method A) and 67% (Method B). White solid, mp 67 - 69 °C. $[\alpha]_D^{25}$ = -18 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): *δ* δ 8.07-7.98 (m, 2H), 7.55-7.44 (m, 3H), 5.82 (d, *J* 9.3 Hz, 1H), 5.29-5.15 (m, 1H), 4.16 (q, *J* 7.1 Hz, 2H), 1.91-1.73 (m, 3H), 1.25 (t, *J* 7.1 Hz, 3H), 1.00 (d, *J* 6.1 Hz, 6H).^{13}C NMR (50 MHz, $CDCl_3$): *δ* 165.93, 164.80, 156.08, 131.73, 128.99, 126.86, 123.64, 61.40, 52.16, 38.80, 25.00, 15.15, 14.44, 11.26. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{16}H_{21}N_3NaO_3$ 326.1481, found 326.1477.

Ethyl (*R*)-*N*-[2-(benzylthio)-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (4a). Yield: 40% (Method A) and 54% (Method B). White solid, mp 79 – 81 °C. $[\alpha]_D^{25}$ = -11 (*c* 1.0, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 8.04-7.94 (m, 2H), 7.57-7.43 (m, 3H), 7.32-7.21 (m, 5H), 5.70 (d, *J* 9.2 Hz, 1H), 5.36-5.24 (m, 1H), 4.16 (q, *J* 7.1 Hz, 2H), 3.70 (s, 2H), 3.06-2.95 (m, 2H), 1.25 (t, *J* 7.1 Hz, 3H).^{13}C NMR (50 MHz, $CDCl_3$): *δ* 165.23, 165.17, 155.75, 137.26, 131.90, 129.01, 128.90, 128.61, 127.28, 126.95, 123.42, 61.65, 47.23, 36.42, 34.43, 14.47. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{20}H_{21}N_3NaO_3S$ 406.1201, found 406.1221.

Ethyl (*S*)-*N*-[3-(methylthio)-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl]carbamate (5a). Yield: 58% (Method A) and 63% (Method B). White solid, mp 81 - 83 °C, $[\alpha]_D^{20}$ = -32 (*c* 1.0, AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10-7.96 (m, 2H), 7.59-7.42 (m, 3H), 5.57-5.48 (m, 1H), 5.38- 5.21 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 2.65 (t, *J* 7.2 Hz, 2H), 2.43-2.30 (m, 1H), 2.29-2.17 (m, 1H), 2.12 (s, 3H), 1.26 (t, *J* 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): *δ* 166.02, 165.15, 155.87, 131.83, 129.03, 126.98, 123.69, 61.59, 47.00, 33.13, 29.90, 15.48, 14.47. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{15}H_{19}N_3NaO_3S$ 344.1045, found 344.1043.

Ethyl (*R*)-*N*-[1-(5-phenyl-1,3,4-oxadiazol-2-yl)-2-(phenylselanyl)ethyl]carbamate (6a). Yield: 51% (Method A) and 52% (Method B). White solid, mp 89 - 91 °C, $[\alpha]_D^{20}$ = -3 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (d, *J* 8.0 Hz, 2H), 7.52-7.40 (m, 5H), 7.11 (d, *J* 7.0 Hz, 2H), 5.95 (d, *J* 9.0 Hz, 1H), 5.49-5.38 (m, 1H), 4.14 (q, *J* 7.1 Hz, 2H), 3.50 (d, *J* 5.9 Hz, 2H), 1.25 (t, *J* 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 164.96, 155.56, 133.60, 131.71, 129.13, 128.82, 128.15, 127.59, 126.85, 123.37, 61.53, 47.88, 31.58, 14.40.^{77}Se (76,28 MHz, $CDCl_3$) δ 263.5 (*vs.* PhSeSePh at 463.0 ppm as an external standard)[1]. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{19}H_{19}N_3NaO_3Se$ 440.0489, found 440.0490.

Ethyl (*S*)-*N*-[-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (1b). Yield: 45% (Method A) and 63% (Method B). Yellow solid, mp 93 - 95 °C. $[\alpha]_D^{25}$= -10 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* 8.1 Hz, 2H), 7.29 (d, *J* 8.1 Hz, 2H), 5.37 (br s, 1H), 5.24–5.13 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 2.42 (s, 3H), 1.66 (d, *J* 7.0 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.73, 165.28, 155.67, 142.34, 129.71, 126.87, 121.01, 61.43, 43.66, 21.54, 19.81, 14.49. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{14}N_{17}N_3NaO_3$ 298.1168, found 298.1170.

Ethyl (*S*)-*N*-[2-phenyl-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (2b). Yield: 40% (Method A) and 72% (Method B). White solid, mp 120 - 122 °C, $[\alpha]_D^{25}$ = -21 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.84 (d, *J* 8.1 Hz, 2H), 7.29-7.23 (m, 5H), 7.15 (d, *J* 6.6 Hz, 2H), 5.57 (d, *J* 8.8 Hz, 1H), 5.41 (br s, 1H), 4.11 (q, *J* 6,8Hz, 2H), 3.35 - 3.28 (m, 2H), 2.41 (s, 3H), 1.21 (t, *J* 6.8 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 165.64, 165.10, 155.76, 142.37, 135.30, 129.67, 129.28, 128.63, 127.18, 126.83, 120.71, 61.42, 48.83, 39.84, 21.54, 14.41. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{20}N_{21}N_3NaO_3$ 374.1481, found 374.1494.

Ethyl (*S*)-*N*-[3-methyl-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)butyl]carbamate (3b). Yield: 41% (Method A) and 60% (Method B). White solid, mp 84 - 86 °C. $[\alpha]_D^{25}$ = -15 (*c* 1,0; AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, *J* 8.1 Hz, 2H), 7.30 (d, *J* 8.1 Hz, 2H), 5.70 (d, *J* 9.3 Hz, 1H), 5.15-5.02 (m, 1H), 4.15 (q, *J* 7.0 Hz, 2H), 2.42 (s, 3H), 2.05 (s, 1H), 1.66-1.48 (m, 1H), 1.25 (t, *J* 7.0 Hz, 3H), 0.96 (t, *J* 7.2 Hz, 6H).^{13}C NMR (50 MHz, $CDCl_3$): δ 165.65, 164.88, 156.09, 142.25, 129.61, 126.73, 120.73, 61.28, 52.06, 38.68, 24.90, 21.50, 15.10, 14.38, 11.22. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{17}N_{23}N_3NaO_3$ 340.1637, found 340.1654.

Ethyl (*R*)-*N*-[2-(benzylthio)-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (4b). Yield: 30 % (Method A)and 55 % (Method B). White solid, mp 88 - 90 °C. $[\alpha]_D^{25}$ = -5,0 (*c* 1,0; AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.91 (d, *J* 8.2 Hz, 2H), 7.35-7.28 (m, 6H), 5.60-5.52 (m, 1H), 5.37-5.26 (m, 1H), 4.18 (q, *J* 7.1 Hz, 2H), 3.70 (d, *J* 5.7 Hz, 2H), 3.02 (dd, *J* 6.1, 1.8 Hz, 2H), 2.44 (s, 3H), 1.28 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.30, 165.18, 155.70, 137.38, 131.84, 129.00, 128.90, 128.60, 127.28, 126.99, 123.62, 61.63, 47.53, 42.63, 36.62, 34.69, 14.45. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{21}H_{23}N_3NaO_3S$ 420.1358, found 420.1365.

Ethyl (*S*)-*N*-[3-(Methylthio)-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)propyl]carbamate (5b). Yield: 35% (Method A) and 64% (Method B). White solid, mp 90 - 92 °C. $[\alpha]_D^{25}$ = -5,0 (*c* 1,0 AcOEt). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.91 (d, *J* 8.1 Hz, 2H), 7.29 (d, *J* 8.1 Hz, 2H), 5.50 (br s, 1H), 5.32-5.25 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 2.64 (t, *J* 7.2 Hz, 2H), 2.42 (s, 3H), 2.39-2.30 (m, 1H), 2.27-2.16 (m, 1H), 2.12 (s, 3H), 1.26 (t, *J* 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 165.72, 165.31,

155.89, 142.44, 129.74, 126.95, 120.91, 61.58, 47.01, 33.18, 29.90, 21.54, 15.48, 14.47. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{16}H_{21}N_3NaO_3S$ 358.1201, found 358.1220.

Ethyl (*R*)-*N*-[2-(phenylselanyl)-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (6b). Yield: 66% (Method A) and 54% (Method B). White solid, mp 107 - 109 °C. $[\alpha]_D^{25}$= -4,0 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* 8.0 Hz, 2H), 7.47 (d, *J* 6.5 Hz, 2H), 7.26 (d, *J* 8.0 Hz, 2H), 7.16-7.07 (m, 3H), 5.85 (d, *J* 8.5 Hz, 1H), 5.41 (br s, 1H), 4.14 (q, *J* 7.0 Hz, 2H), 3.49 (d, *J* 5.6 Hz, 2H), 2.41 (s, 3H), 1.25 (t, *J* 7.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 165.16, 164.70, 155.61, 142.33, 133.65, 129.56, 129.16, 128.19, 127.63, 126.86, 120.61, 61.56, 47.88, 31.68, 21.57, 14.43. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{20}H_{21}N_3NaO_3Se$ 454.0646, found 454.0616.

Ethyl (*S*)-*N*-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)ethyl]carbamate (1c). Yield: 40% (Method A) and 57% (Method B). Yellow solid, mp 88 - 91°C, $[\alpha]_D^{25}$ = -45 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, DMSO): δ7.86 (d, *J* 8.6 Hz, 2H), 7.15 (br s, 1H), 7.01 (d, *J* 8.6 Hz, 1H), 4.21-4.12 (m, 1H), 4.00 (q, *J* 7.0 Hz, 1H), 3.82 (s, 3H), 1.30 (d, *J* 7.1 Hz, 2H), 1.17 (t, *J*= 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO): δ= 171.96, 164.74, 161.85, 155.57, 129.17, 124.62, 113.53, 59.64, 55.26, 48.56, 18.27, 14.46. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{14}N_{17}N_3NaO_4$ 314.1117, found 314.1132.

Ethyl (*S*)-*N*-[-1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-(phenyl)ethyl]carbamate (2c). Yield: 46% (Method A) and 70% (Method B). White solid, mp 106 - 108 °C. $[\alpha]_D^{25}$ = -17 (*c* 1,0; AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, *J* 8.8 Hz, 2H), 7.31-7.21 (m, 3H), 7.20- 7.10 (m, 2H), 6.98 (d, *J* 8.8 Hz, 2H), 5.51-5.33 (m, 2H), 4.12 (q, *J* 7.2 Hz, 2H), 3.87 (s, 3H), 3.31 (d, *J* 5.9 Hz, 2H), 1.22 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.40, 164.97, 162.53, 155.69, 135.46, 129.36, 128.71, 128.67, 127.22, 116.24, 114.54, 61.47, 55.42, 48.99, 40.06, 14.45.HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{20}N_{21}N_3NaO_4$ 390.1430, found 390.1436.

Ethyl (*S*)-*N*-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-3-(methyl)butyl]carbamate (3c). Yield: 46% (Method A) and 70% (Method B). White solid, mp 105 - 107 °C. $[\alpha]_D^{25}$ = -8.0 (*c* 1.0. AcOEt). ^{1}H NMR (400 MHz, DMSO): δ 7.91 (d, *J* 8.9 Hz, 2H), 7.76 (br s, 1H), 7.14 (d, *J* 8.9 Hz, 1H), 4.78 (t, *J* 8.0 Hz, 1H), 4.03 (q, *J* 7.0 Hz, 2H), 3.85 (s, 3H), 2.05-1.96 (m, 1H), 1.60-1.49 (m, 1H), 1.32-1.20 (m, 1H), 1.17 (t, *J* 7.0 Hz, 3H), 0.91 - 0.82 (m, 6H).^{13}C NMR (100 MHz, DMSO): δ 165.51, 163.83, 162.03, 156.08, 128.30, 115.62, 114.88, 60.19, 55.50, 51.67, 36.97, 24.82, 15.23, 14.49, 10.72. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{17}N_{23}N_3NaO_4$ 356.1586, found 356.1569.

Ethyl (*R*)-*N*-[2-(benzylthio)-1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)ethyl]carbamate (4c). Yield: 35% (Method A)and 53% (Method B). White solid, mp 75 - 77 °C. $[\alpha]_D^{25}$= -6.0(*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.95 (d, *J* 8.9 Hz, 2H), 7.33-7.25 (m, 5H), 6.99 (d, *J* 8.9 Hz, 2H), 5.66 (d, *J* 8.4 Hz, 1H), 5.37-5.18 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 3.88 (s, 3H), 3.71 (s, 2H), 3.02 (dd, *J* 6.2, 2.0 Hz, 2H), 1.27 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 165.14, 164.71, 162.47, 155.77, 137.35, 128.92, 128.76, 128.61, 127.27, 115.99, 114.47, 61.63, 55.43, 47.30, 36.51, 34.58, 14.48. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{21}H_{23}N_3NaO_4S$ 436.1307, found 436.1289.

Ethyl (*S*)-*N*-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl]carbamate (5c). Yield: 42% (Method A) and 60% (Method B). White solid, mp 52 - 54 °C. $[\alpha]_D^{25}$ = -11 (*c* 1.0

AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.95 (d, *J* 8.8 Hz, 2H), 6.98 (d, *J* 8.8 Hz, 2H), 5.78-5.69 (m, 1H), 5.32-5.23 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 3.87 (s, 3H), 2.65 (t, *J* 7.3 Hz, 2H), 2.40-2.30 (m, 1H), 2.28-2.17 (m, 1H), 2.12 (s, 3H), 1.26 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 165.45, 165.00, 162.40, 155.91, 128.65, 115.99, 114.42, 61.45, 55.36, 46.81, 32.95, 29.81, 15.39, 14.43. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{16}H_{21}N_3NaO_4S$ 374.1150, found 374.1129.

Ethyl (*R*)-*N*-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-(phenylselanyl)ethyl]carbamate (6c). Yield: 42% (Method A) and 60% (Method B). White solid, mp 101 - 103 °C. $[\alpha]_D^{25}$ = -11 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.82 (d, *J* 8.3 Hz, 2H), 7.47 (d, *J* 7.2 Hz, 2H), 7.16-7.08 (m, 3H), 6.94 (d, *J* 8.3 Hz, 2H), 6.02 (d, *J* 8.7 Hz, 1H), 5.39 (br s, 1H), 4.13 (q, *J* 7.0 Hz, 2H), 3.85 (s, 3H), 3.49 (d, *J* 5.7 Hz, 2H), 1.24 (t, *J* 7.0 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ= 164.82, 164.41, 162.23, 155.58, 133.48, 129.05, 128.57, 128.25, 127.47, 115.77, 114.20, 61.41, 55.29, 47.81, 31.40, 14.35. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{20}H_{21}N_3NaO_3Se$ 470.0595, found 470.0598.

Ethyl (*S*)-*N*-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)ethyl]carbamate (1d). Yield: 44% (Method A)and 50% (Method B). White solid, mp 95 - 97 °C. $[\alpha]_D^{25}$= -17 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98 (d, *J* 8.8 Hz, 2H), 7.48 (d, *J* 8.8 Hz, 2H), 5.46 - 5.37 (m, 1H), 5.27-5.15 (m,1H), 4.17 (q, *J* 7.1 Hz, 2H), 1.68 (d, *J* 7.0 Hz, 2H), 1.27 (t, *J* 7.1 Hz, 3H), 1.26 (t, *J* 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.03, 165.12, 155.68, 131.80, 129.01, 126.94, 123.68, 61.45, 43.58, 19.76, 14.49. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{13}H_{14}ClN_3NaO_3$ 318.0621, found 318.0616.

Ethyl (*S*)-*N*-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2-(phenyl)ethyl]carbamate (2d). Yield: 35% (Method A) and 62% (Method B). White solid, mp 129 - 132 °C. $[\alpha]_D^{25}$ = -7.0 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (d, *J* 8.4 Hz, 2H), 7.43 (d, *J* 8.5 Hz, 2H), 7.32-7.12 (m, 5H), 5.85 (d, *J* 8.7 Hz, 1H), 5.50-5.29 (m, *J* 14.4 Hz, 1H), 4.11 (q, *J* 7.1 Hz, 2H), 3.33 (d, *J* 6.6 Hz, 2H), 1.20 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.12, 164.02, 155.72, 137.96, 135.24, 129.25, 129.18, 128.55, 128.02, 127.12, 121.84, 61.36, 48.75, 39.57, 14.35. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{19}H_{18}ClN_3NaO_3$ 394.0934, found 394.0899.

Ethyl (*S*)-*N*-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-3-(methyl)butyl]carbamate (3d). Yield: 38% (Method A) and 42% (Method B). White solid, mp 89 - 91 °C. $[\alpha]_D^{25}$ = -5.0 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (d, *J* 8.4 Hz, 2H), 7.47 (d, *J* 8.4 Hz, 2H), 5.48 (d, *J* 7.5 Hz, 1H), 5.14 (br s, 1H), 4.16 (d, *J* 7.1 Hz, 2H), 1.88-1.72 (m, 2H), 1.25 (t, *J* 7.1 Hz, 2H), 1.00 (d, *J* 6.3 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 167.21, 164.05, 155.91, 138.03, 129.35, 128.15, 122.13, 61.41, 46.01, 42.68, 24.59, 22.58, 21.80, 14.44. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{16}H_{20}ClN_3NaO_3$ 360.1091, found 360.1078.

Ethyl (*R*)-*N*-[2-(benzylthio)-1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)ethyl]carbamate (4d). Yield: 35% (Method A) and 52% (Method B). Yellow solid, mp 85 - 87°C. $[\alpha]_D^{25}$ = -7.0 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94 (d, *J* 8.5 Hz, 2H), 7.47 (d, *J* 8.5 Hz, 2H), 7.28 (s, 5H), 5.74 (d, *J* 8.6 Hz, 1H), 5.39-5.22 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 3.72 (s, 2H), 3.02 (d, *J* 6.2 Hz, 2H), 1.27 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.63, 164.53, 155.91, 138.38, 137.45, 129.58, 129.06, 128.79, 128.40, 127.48, 122.13, 61.84, 47.46, 36.68, 34.62, 14.64. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{20}H_{20}ClN_3NaO_3S$ 440.0812, found 440.0833.

Ethyl (*S*)-*N*-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-3-(methylthio)ethyl]carbamate (5d). Yield: 30% (Method A) and 43% (Method B). White solid, mp 57 - 60 °C. $[\alpha]_D^{25}$ = -4.0 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.96 (d, *J* 8.5 Hz, 2H), 7.48 (d, *J* 8.5 Hz, 2H), 5.61 (d, *J* 8.8 Hz, 1H), 5.38 - 5.28 (m, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 2.65 (t, *J* 7.2 Hz, 2H), 2.42- 2.31 (m, *J* 13.8 Hz, 1H), 2.29-2.18 (m, *J* 7.1 Hz, 1H), 2.12 (s, 3H), 1.26 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.22, 164.31, 155.88, 138.20, 129.42, 128.20, 122.02, 61.60, 46.83, 32.88, 29.83, 15.46, 14.46. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{15}H_{18}ClN_3NaO_3S$ 378.0655, found 378.0660.

Ethyl (*R*)-*N*-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2-(phenylselanyl)ethyl]carbamate (6d). Yield: 50% (Method A) and 47% (Method B). White solid, mp 103 - 105 °C. $[\alpha]_D^{25}$ = -7.0 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ =7.82 (d, *J* 8.6 Hz, 2H), 7.47–7.44 (m, 4H), 7.15–7.10 (m, 3H), 5.68 (br s, 1H), 5.41 (br s, 1H), 4.14 (q, *J* 7.1 Hz, 2H), 3.49 (d, *J* 5.9 Hz, 2H), 1.25 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.21, 164.26, 155.54, 138.16, 133.75, 129.33, 129.24, 128.22, 127.74, 122.01, 61.70, 48.01, 31.74, 14.46. HRMS (TOF MS ESI+) $[M+Na]^+$: Calcd for $C_{19}H_{18}ClN_3NaO_3Se$ 474.0100, found 474.0083.

Acknowledgements

The authors gratefully acknowledge CNPq, CAPES, FAPERGS (PRONEM- 11/2080-9) and FAPESP (2013/06558-3), for financial support.

Supplementary Information

General experimental procedures, ^{1}H and ^{13}C NMR and HRMS (TOF MS ESI+) data for compounds are available as supplementary information.

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