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Microwave-Assisted Synthesis of Unsymmetrical 5-Phenyl-1,3,4-oxadiazoles Containing Bis(carboxymethyl)amino Group

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Abstract: New derivatives of 5-phenyl-1,3,4-oxadiazole substituted at position 2 with (bromomethyl)-phenyl or bromoalkyl groups were obtained via microwave-assisted cyclodehydration of unsymmetrical *N*,*N*′-diacylhydrazines. Then, bromine-containing oxadiazoles were substituted with diisopropyl iminodiacetate, yielding the corresponding ester derivatives, which were subsequently hydrolyzed in an aqueous methanol solution. The cleavage of the ester group resulted in the formation of the appropriate 5-phenyl-1,3,4-oxadiazoles bearing bis(carboxymethyl)amino groups in satisfactory yields. The structures of all products were confirmed by typical spectroscopic methods including 1H and 13C NMR, and HRMS.

Keywords: *N*,*N*′-diacylhydrazines; cyclization; microwaves; 1,3,4-oxadiazoles; substitution; diisopropyl iminodiacetate; hydrolysis

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1. Introduction

Oxadiazoles belong to the group of heterocyclic compounds which contain two nitrogen atoms and one oxygen atom. Due to the position of heteroatoms in the ring, they comprise few isomers [1]. 1,2,4-Oxadiazoles and 1,3,4-oxadiazoles belong to the group of the most frequently studied compounds due to their high biological activity and good stability [2]. These derivatives have anti-inflammatory, analgesic [3], anticancer [4], antibacterial [5], antifungal [6], antiviral [7], or blood-pressure-lowering effects [8]. Oxadiazoles are also successfully used in agriculture as herbicides, insecticides, and plant protection agents against bacteria, viruses, and fungi (Figure 1) [9–12]. Conjugated macrocyclic arrangements containing 1,3,4-oxadiazole core exhibit interesting electron-transfer or luminescent properties and are applied in the production of different types of conducting systems including laser dyes, scintillators, optical brighteners, or organic light-emitting diodes [13–16]. Furthermore, in materials science, compounds of this type are used in the production of blowing agents, heat-resistant polymers, and anti-corrosion agents [17–20]. 1,3,4-Oxadiazoles can be obtained by a number of cyclization methods. The most popular procedures include the cyclodehydration reaction of diacylhydrazines with sulfuric acid [21], thionyl chloride [22], polyphosphoric acid [23], phosphoryl chloride [24], trifluoromethanesulfonic anhydride [25], phosphorus pentoxide [26], or triphenylphosphine derivatives [27]. Other methods of effective synthesis of 1,3,4-oxadiazoles also include the oxidative cyclization of *N*-acylhydrazones under the action of bromine [28], potassium permanganate [29], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [30], or cerium ammonium nitrate [31].

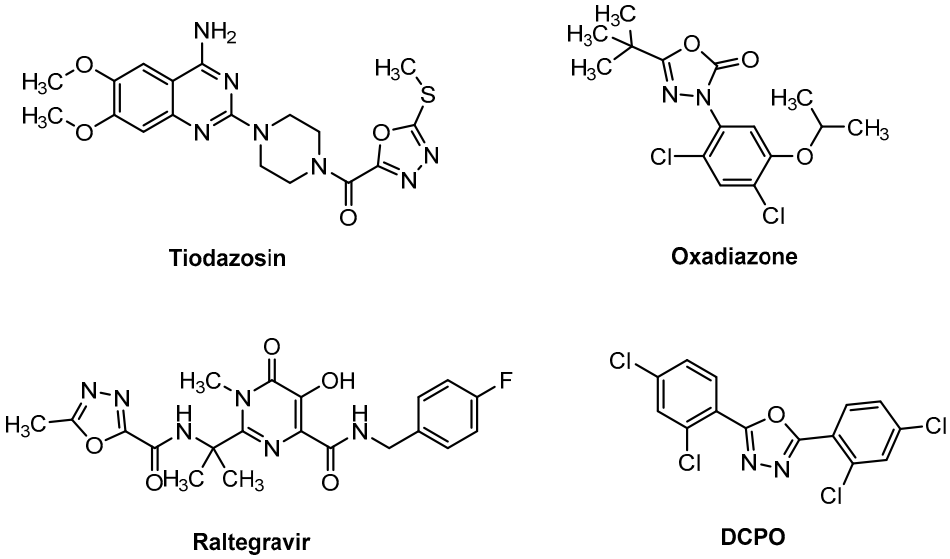


Figure 1. Biologically active 1,3,4-oxadiazoles used in agriculture and medicine [32].

Micronutrient chelates belong to complex compounds in which the organic ligand is connected to the metal ion using more than one coordination center. In modern agriculture, they are successfully used as effective fertilizers. One of the main limitations in plant cultivation is the various types of micronutrient deficiencies, which require the application of substances containing a given element in their structure. The most commonly used micronutrients include copper (Cu^{2+}), manganese (Mn^{2+}), iron (Fe^{3+}), and zinc (Zn^{2+}). On the other hand, organic compounds that may act as potential ligands usually contain electron-donating groups, including aminopolycarboxylic functionality. The currently used compounds with metal cation complexing properties comprise ethylenediaminetetraacetic acid (EDTA), ethylenediamine-di-(*o*-hydroxyphenylacetic acid) (EDDHA), ethylenediamine-di-(5-carboxy-2-hydroxyphenyl)acetic acid (EDDCHA), nitrilotriacetic acid (NTA), diethylenetriaminepentaacetic acid (DTPA), glucoheptanoic acid, and citric acid [33].

An interesting group of new organic ligands with complexing properties could constitute heterocyclic arrangements such as 1,3,4-oxadiazoles, substituted with the bis(carboxymethyl)amino group. It seems to be quite probable that these hybrids, unknown in the literature to date, could exhibit even stronger properties toward complexation due to the presence of ring oxygen and nitrogen heteroatoms with lone electron pairs. Previously, we elaborated the methodology for the construction of symmetrical derivatives of 2,5-dialkyl-1,3,4-oxadiazoles substituted with bis(carboxymethyl)amino groups at the terminal alkyl positions [34]. This study initiated a broad research program devoted to the synthesis and properties of new five-membered heterocyclic ligands, which may be of interest to researchers in agriculture who are still looking for new, effective micronutrient chelates. The work presented here describes a convenient and practical methodology for preparation of 5-phenyl-1,3,4-oxadiazoles connected to the bis(carboxymethyl)amino group via benzylene and alkylene linkers. The initial concept of the synthesis comprised the preparation of intermediate unsymmetrical *N*,*N*′-diacylhydrazines, supplemented with bromine at the terminal alkyl position, their cyclization to 1,3,4-oxadiazole derivatives, and the subsequent substitution with iminodiacetic acid (Figure 2).

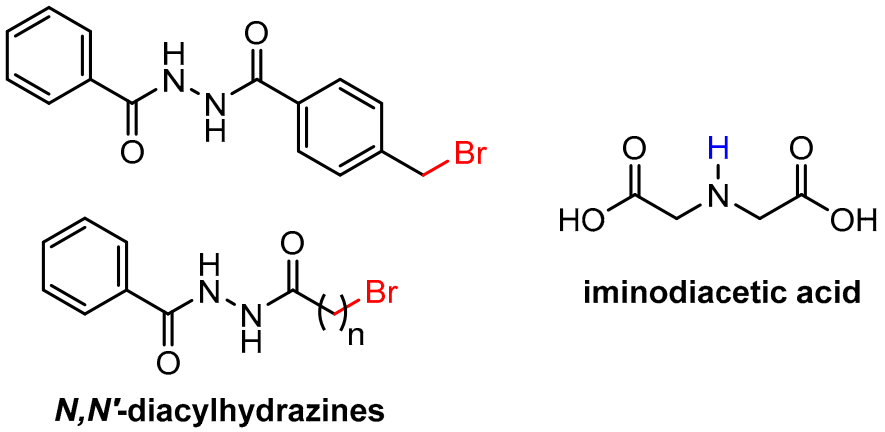
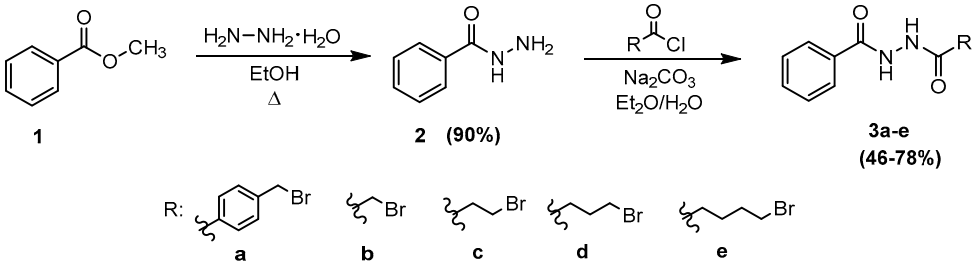


Figure 2. Key intermediates in the synthesis of new 5-phenyl-1,3,4-oxadiazoles containing bis(carboxymethyl)amino group: unsymmetrical *N*,*N*′-diacylhydrazines and iminodiacetic acid.

2. Results

The target 1,3,4-oxadiazoles bearing bis(carboxymethyl)amino groups were synthesized according to a few-step procedure. The first step was the preparation of benzhydrazide (**2**) by means of methyl benzoate (**1**), hydrazine hydrate and ethanol, used in this case as a solvent. The reaction proceeded at reflux for about 10 h (Scheme 1) [35]. The main product was obtained in a high yield of 90% without the need of purification.



Scheme 1. Synthesis of benzhydrazide (**2**) and unsymmetrical *N*,*N*′-diacylhydrazine derivatives (**3a**–**e**). Reaction conditions: step 1: methyl benzoate (**1**, 15 mL, 0.12 mol), hydrazine hydrate (11.96 mL, 0.24 mol), EtOH (50 mL), reflux, 10 h; step 2: benzhydrazide (**2**, 0.02 mol), acid chloride (0.02 mol), Et_2O (40 mL), Na_2CO_3 (0.02 mol), H_2O (15 mL), 1 h.

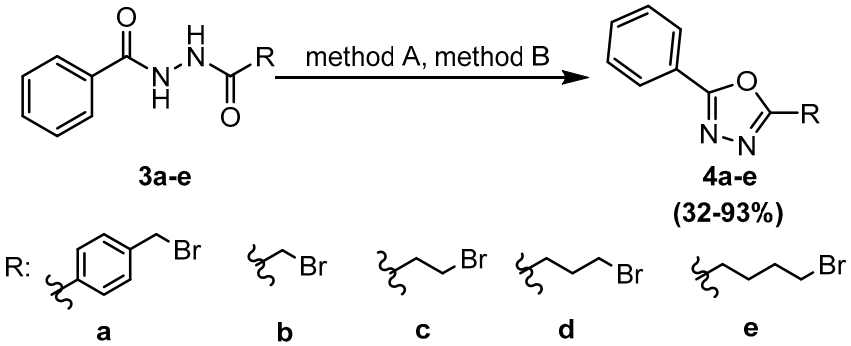
In the next step, the benzhydrazide (**2**) formed was reacted with commercially available 4-bromomethylbenzoyl chloride (a) or alkanecarboxylic acid chlorides (b–e), which differed in the length of the alkyl chain and contained a bromine substituent in the terminal position (Scheme 1). We applied similar reaction conditions which were elaborated previously while working on the preparation of symmetrical *N*,*N*′-diacylhydrazine derivatives [34]. The reaction was conducted at room temperature using diethyl ether as a solvent in which the benzhydrazide substrate was suspended. Due to the high reactivity of the acid chlorides, they were carefully added to the reaction mixture. Sodium carbonate dissolved in a small amount of water was used as the base to neutralize the evolving hydrogen chloride. The crude products were recrystallized by means of methanol or ethanol. The yields of the resulted hydrazine derivatives (**3a**–**e**) varied from 46% to 78% (Table 1, Entries 1–5).

Table 1. Unsymmetrical *N*,*N*′-diacylhydrazine derivatives (**3a**–**e**) derived from benzhydrazide and acid chlorides.

Entry	n [(a)]	R	Product	Yield (%)
1	1	4-(Bromomethyl)phenyl	**3a**	78
2	1	Bromomethyl	**3b**	46
3	2	2-Bromoethyl	**3c**	65
4	3	3-Bromopropyl	**3d**	69
5	4	4-Bromobutyl	**3e**	71

[(a)] n—number of -CH_2- groups.

The formation of 1,3,4-oxadiazole derivatives (**4a**–**e**) consisted in the reaction of *N*,*N*′-diacylhydrazines **3a**–**e** with a range of cyclodehydrating agents such as phosphorus pentachloride (PCl_5), thionyl chloride ($SOCl_2$), perchloric acid ($HClO_4$), phosphorus pentoxide (P_2O_5), and phosphoryl trichloride ($POCl_3$). Among them, phosphoryl trichloride $POCl_3$, acting both as a reagent and a solvent, proved to be an effective agent for most of the products (**4a**–**b**, **4d**–**e**). Only in the case of 2-(2-bromoethyl)-5-phenyl-1,3,4-oxadiazole (**4c**) was a better yield obtained with the use of phosphorus pentoxide P_2O_5 in toluene. Regardless of the method used, the reaction mixture was heated to 70 °C, and the progress of the reaction was controlled by TLC (Scheme 2). Heating to a higher temperature most likely caused decomposition of the formed 1,3,4-oxadiazole product. The duration of the reaction depended on the type of substrate used.



Scheme 2. Synthesis of unsymmetrical 1,3,4-oxadiazole derivatives (**4a**–**e**). Reaction conditions: method A: *N*,*N*′-diacylhydrazine (**3a**–**e**, 0.008 mol), $POCl_3$ (0.28 mol), 70 °C, 1–12 h; method B: *N*,*N*′-diacylhydrazine (**3a**–**e**, 0.008 mol), P_2O_5 (0.02 mol), toluene (100 mL).

The best result was achieved for the cyclization reaction of the *N*,*N*′-diacylhydrazine derivative containing the 4-(bromomethyl)phenyl group (**3a**), where the time needed for complete reaction of the substrate was about 3 h (Table 2, Entry 1). In the case of transformations making use of *N*,*N*′-diacylhydrazines-bearing bromoalkyl substituents (**3b**–**e**), reaction times were considerably longer, and even reaching 8 h (Table 2, Entries 2–5). Thus, we decided to carry out the same reactions under microwave irradiation (Table 2, Entries 6–10). Conducting the reaction using a microwave reactor was based on preliminary optimization of the process parameters. For this purpose, two different modes offered by the CEM device software (Synergy 1.58, Version: 201A19) were used: SPS and Dynamic. During the process optimization, the impact of the microwave heating power was also tested. It was found that setting the power higher than 100 W (130, 150, 200 W) resulted in too intense heating of the mixture and the release of $POCl_3$ from the reaction vessel. The SPS method, which is based on intensive heating of the reaction mixture to the indicated temperature, was ineffective due to the temporary activation of microwave radiation and too large temperature changes. In contrast, the Dynamic method (100 W, 70 °C) was better due to more precise control of the temperature during the reaction and constant supply of the appropriate amount of microwave radiation. All reactions using a microwave reactor

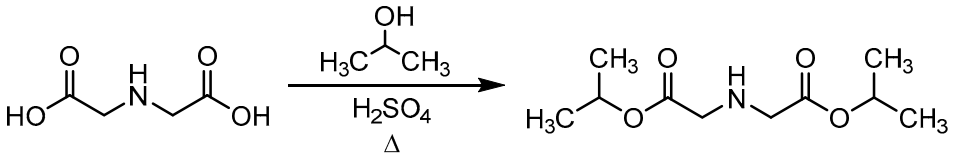
were carried out with a reflux reaction device. Studies have shown that the use of MW heating contributes to a significant reduction in the reaction time (1–2.5 h), while the yields of products remain in fact at the same level in comparison to traditional methods. The best yield was achieved in the case of 2-[(4-bromomethyl)phenyl]-5-phenyl-1,3,4-oxadiazole (**4a**), in which three aromatic rings are directly conjugated (93%, Table 2, Entry 6). The yields of the less conjugated 2-bromoalkyl-5-phenyl-1,3,4-oxadiazoles were at the moderate level of 38–75% (Table 2, Entries 7–10). The resulting final products **4a**–**e** were purified by column chromatography using 2:1 hexane:ethyl acetate by volume as the mobile phase.

Table 2. 5-Phenyl-1,3,4-oxadiazole derivatives (**4a**–**e**) obtained from cyclization of the corresponding *N*,*N*′-diacylhydrazines.

Entry	Conditions	n [(c)]	R	Product	Time (h)	Yield (%)
1	Δt [(a)]	1	4-(Bromomethyl)phenyl	**4a**	3	90
2	Δt	1	Bromomethyl	**4b**	8	60
3	Δt	2	2-Bromoethyl	**4c**	4	32
4	Δt	3	3-Bromopropyl	**4d**	6	73
5	Δt	4	4-Bromobutyl	**4e**	6	62
6	MW [(b)]	1	4-(Bromomethyl)phenyl	**4a**	1	93
7	MW	1	Bromomethyl	**4b**	2.5	65
8	MW	2	2-Bromoethyl	**4c**	2	38
9	MW	3	3-Bromopropyl	**4d**	1.5	75
10	MW	4	4-Bromobutyl	**4e**	1.5	64

[(a)] Conventional heating: Δt, oil bath, 70 °C; [(b)] MW heating: 100 W, 70 °C; [(c)] number of -CH_2- groups.

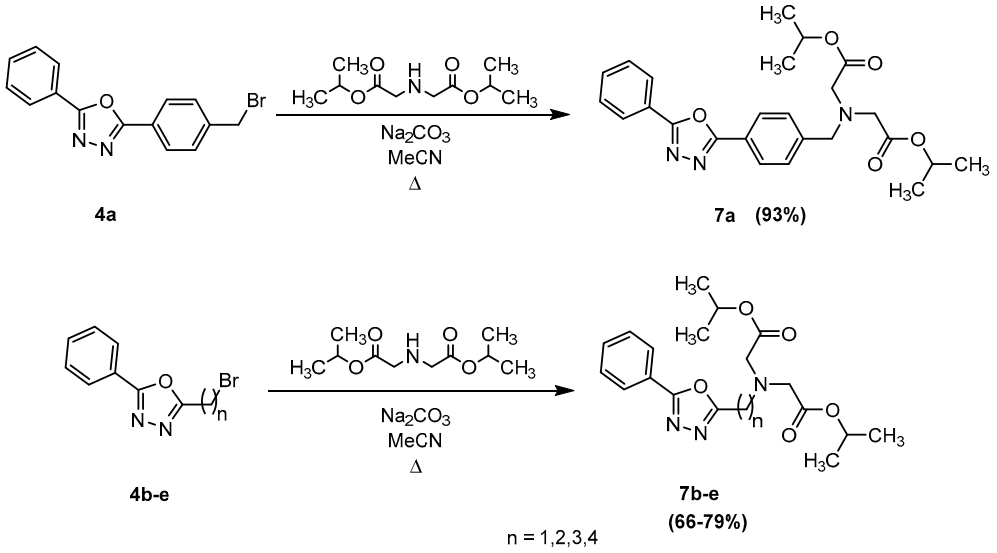
The next stage comprised the substitution of the bromine-containing 1,3,4-oxadiazoles (**4a**–**e**) in order to introduce the bis(carboxymethyl)amino group. The typical methodology for introducing such a group into the leading organic unit involves heating alkyl or arylalkyl halides with iminodiacetic acid in a methanol solution of potassium hydroxide [36]. Thus, we decided to check if such a procedure could be applied for the direct substitution of a model derivative of 2-[(4-bromomethyl)phenyl]-5-phenyl-1,3,4-oxadiazole (**4a**). Unfortunately, the reaction did not proceed even with the use of microwave irradiation. In our previous research on the synthesis of symmetrical 1,3,4-oxadiazole derivatives with carboxymethylamino groups, we used diisopropyl ester of iminodiacetic acid (**6**), which showed high reactivity towards oxadiazole derivatives [34]. The synthesis of such a reagent was carried out using iminodiacetic acid and isopropanol in the presence of an acidic catalyst such as concentrated sulfuric acid (Scheme 3).



5 **6** **(52%)**

Scheme 3. Synthesis of diisopropyl iminodiacetate (**6**). Reaction conditions: iminodiacetic acid (**5**, 15.0 g, 0.11 mol), isopropanol (120 mL), H_2SO_4 (7.5 mL), reflux, 12 h.

Having ester **6** in hand, we were able to study the substitution reaction in a series of bromine-containing 1,3,4-oxadiazoles (**4a**–**e**) (Scheme 4). In order to determine the optimal conditions, the reaction between 2-[(4-bromomethyl)phenyl]-5-phenyl-1,3,4-oxadiazole (**4a**) and diethyl iminodiacetate (**6**) was first examined (Table 3). The following agents influencing the reaction yield were tested: bases including triethylamine TEA and sodium carbonate Na_2CO_3, solvents (acetonitrile, DMF), temperature, and type of heating (traditional, MW).



Scheme 4. Synthesis of 1,3,4-oxadiazole derivatives (**7a**–**e**). Reaction conditions: 1,3,4-oxadiazole derivative **4a**–**e** (0.008 mol), diisopropyl iminodiacetate (**6**, 0.008 mol), Na_2CO_3 (0.08 mol), MeCN (50 mL), 80 °C, 8–12 h.

Table 3. Optimization of the reaction for 2-(4-bromomethyl)phenyl-5-phenyl-1,3,4-oxadiazole (**4a**) and diisopropyl iminodiacetate (**6**).

Entry	Solvent	Base	Temperature	Conditions	Yield (%)
1	DMF	TEA	150	Δt [(a)]	49
2	Acetonitrile	TEA	80	Δt	59
4	DMF	TEA	150	MW [(b)]	51
5	Acetonitrile	TEA	80	MW	65
7	DMF	Na_2CO_3	150	Δt	77
8	Acetonitrile	Na_2CO_3	80	Δt	93
10	DMF	Na_2CO_3	150	MW	80
11	Acetonitrile	Na_2CO_3	80	MW	93

[(a)] Conventional heating: Δt, oil bath, 70 °C; [(b)] MW heating: 100 W, 70 °C.

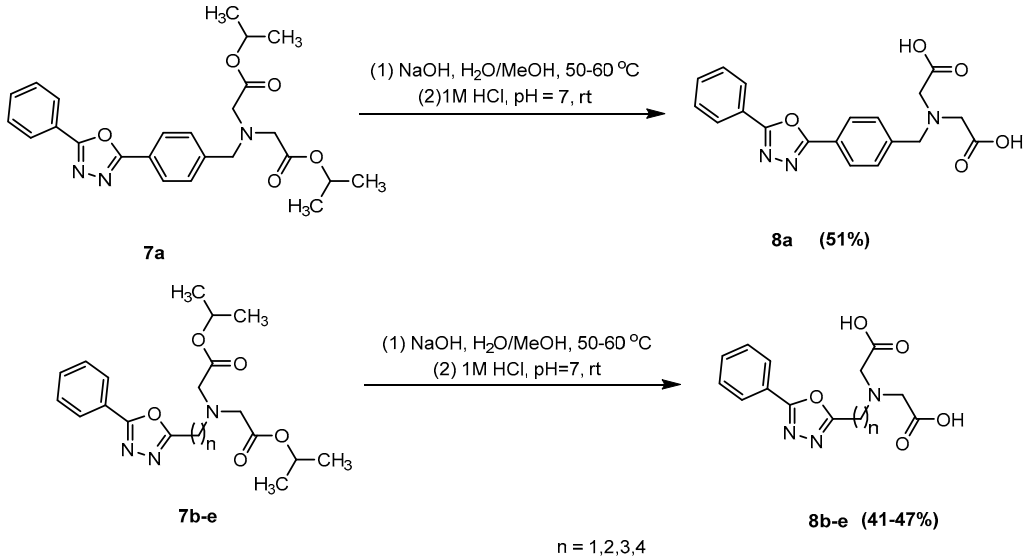
The best results were achieved by conducting the reaction using aprotic acetonitrile as a solvent, and a base in the form of sodium carbonate Na_2CO_3, which also enhanced the elimination of inorganic compounds in the subsequent extraction process (Table 3, Entry 8). The reaction mixture was refluxed for about 8–12 h while the progress of the reaction was monitored by TLC. The use of microwave irradiation at this stage of the synthesis did not improve the reaction rate or the yield of final products. A series of products (**7a**–**e**) was thus obtained with a yield of 66–93% (Table 4, Entries 1–5). All products were purified by column chromatography using silica gel as stationary phase and ethyl acetate as the mobile one.

Table 4. 5-Phenyl-1,3,4-oxadiazole derivatives containing an ester group (**7a**–**e**) formed by substitution with diisopropyl iminodiacetate (**6**).

Entry	n [(a)]	R	Product	Yield (%)
1	1	4-(Bromomethyl)phenyl	**7a**	93
2	1	Bromomethyl	**7b**	79
3	2	2-Bromoethyl	**7c**	69
4	3	3-Bromopropyl	**7d**	71
5	4	4-Bromobutyl	**7e**	66

[(a)] number of -CH_2- groups.

The last step of the synthesis was to carry out hydrolysis in order to restore the carboxyl group from the ester group. Typical acidic hydrolysis conducted in aqueous methanol solution in the presence of a catalytical amount of strong sulfuric acid H_2SO_4 was ineffective; we observed only the partial cleavage of ester groups. Thus, we decided to use alkaline hydrolysis to carry out the reaction for unsymmetrical 1,3,4-oxadiazole derivatives (**7a**–**e**). For this purpose, we used sodium hydroxide NaOH in a molar ratio of 10:1 to the ester, and a mixture of water and methanol as a solvent (Scheme 5). Due to the risk of decomposition of the oxadiazole ring, the reaction mixture was heated in the range of 50–60 °C for about 30 min. The final crude products (**8a**–**e**) were purified by recrystallization from methanol, yielding pure 5-phenyl-1,3,4-oxadiazole derivatives bearing bis(carboxymethy)amino groups in yields varying from 41% to 51% (Table 5, Entries 1–5).



Scheme 5. Synthesis of 2-alkyl-5-phenyl-1,3,4-oxadiazole derivative containing bis(carboxymethyl)amino group (**8a**–**e**). Reaction conditions: ester derivative of 5-phenyl-1,3,4-oxadiazole (**7a**–**e**, 0.26 mmol), NaOH (0.1 g, 2.6 mmol), MeOH (24 mL), H_2O (6 mL), 50–60 °C, 30 min.

Table 5. 5-Phenyl-1,3,4-oxadiazole derivatives containing bis(carboxymethyl)amino group (**8a**–**e**) formed by hydrolysis.

Entry	n [(a)]	R	Product	Yield (%)
1	1	4-(Bromomethyl)phenyl	**8a**	51
2	1	Bromomethyl	**8b**	47
3	2	2-Bromoethyl	**8c**	42
4	3	3-Bromopropyl	**8d**	44
5	4	4-Bromobutyl	**8e**	41

[(a)] number of -CH_2- groups.

The structure of the products was confirmed by nuclear magnetic resonance spectroscopy (1H and 13C NMR) (see Supplementary Materials). Among the 5-phenyl-1,3,4-oxadiazole derivatives containing the ester group (**7a**–**e**) that have not yet been described in the literature, the most specific signals were a doublet at 1.26 ppm and a multiplet at 5.00 ppm for the isopropyl group. The signal, which occurred at 3.50–3.60 ppm, was in turn associated with the iminodiacetate residue. Other signals, which were characteristic of the benzene ring directly attached to the oxadiazole moiety, occurred in the range between 7.50 and 8.16 ppm. The side alkyl chain, which is located between the oxadiazole and the diisopropyl ester fragments, corresponds to signals at 1.00–4.20 ppm. In the case of 13C NMR spectra, one can distinguish two individual signals characteristic of the C2

and C5 carbons of the 1,3,4-oxadiazole ring, which occur in the range between 163.0 and 167.0 ppm. Another characteristic signal is responsible for the carbonyl moiety located at 170.0 ppm. The signals responsible for the ester part of the molecule were located at 22.0 ppm (CH_3) and 68.0 ppm (CH), while the peak at 55.0 ppm was responsible for the carbon of the iminodiacetate part ($N(CH_2)_2<$). Carbon atom signals occurring in the range of 123.0–145.0 ppm corresponded to the benzene ring, while signals in the range of 22.0–60.0 ppm were characteristic of the alkyl chain. The 1H and 13C spectra of the target products (**8a**–**e**) were characterized by the lack of signals characteristic of ester groups. Additionally, high-resolution mass spectra were performed to confirm the structure of the resulting products.

3. Experimental Section

3.1. General Information

All reagents such as methyl benzoate 99% (Acros Organics, Geel, Belgium), hydrazine hydrate conc. 50–60% (Sigma-Aldrich, St. Louis, MO, USA), 4-(bromomethyl)-benzoic acid 98% (Angene, London, UK), and the acid chlorides bromoacetyl chloride 95% (Acros Organics), 3-bromopropionyl chloride 95% (Acros Organics, Geel, Belgium), 4-bromobutyryl chloride 97% (Alfa Aesar, Haverhill, MA, USA), and 5-bromovaleryl chloride 97% (AmBeed, Arlington Heights, IL, USA) were purchased from commercial sources and used without additional purification. Reactions with microwave irradiation were perfomed using CEM Discover apparatus (Matthews, NC, USA) according to the Dynamic method (100 W, 70 °C). Melting points were determined by means of Stuart SMP3 melting point apparatus (Stone, Staffordshire, UK). NMR spectra were performed using an Agilent 400-NMR spectrometer at 25 °C (Agilent Technologies, Waldbronn, Germany) at 400 MHz for ^{1}H, and 100 MHz for ^{13}C, with TMS as the internal standard in $CDCl_3$ or DMSO as solvents. High-resolution mass spectra were recorded using a Waters ACQUITY UPLC/Xevo G2Qt apparatus (Waters Corporation, Milford, MA, USA). Thin-layer chromatography (TLC) was performed on silica gel 60 F254 chromatography plates (Merck, Merck KGa, Darmstadt, Germany), with the use of ethyl acetate or ethyl acetate/hexane (2:1, 1:2 *v*/*v*) as the mobile phases.

3.2. Synthesis and Characterization

3.2.1. Synthesis of Benzhydrazide (**2**)

Methyl benzoate (**1**, 15 mL, 0.12 mol) and hydrazine hydrate (11.96 mL, 0.24 mol) were dissolved in ethanol (50 mL). The mixture was heated to reflux for about 10 h. The content of the flask was then rotary-evaporated, 5 mL of isopropanol was added and heated to reflux for about 5 min. After cooling, 15 mL of hexane was introduced and left in the freezer overnight. The solid was filtered off and air dried.

Benzhydrazide (**2**)

The product was obtained as white solid (14.62 g, 90%); m.p. 114–116 °C [37]. 1H-NMR (400 MHz, DMSO): δ 4.52 (s, 2H), 7.45 (m, 2H), 7.51 (m, 1H), 7.83 (m, 2H), 9.78 (s, 1H); 13C-NMR (100 MHz, DMSO): δ 126.9, 128.3, 131.0, 133.3, 165.9. HRMS (ESI): *m*/*z* calcd for $C_7H_8N_2O + H^+$: 137.0715; found 137.0741.

3.2.2. Synthesis of Unsymmetrical *N*,*N*′-Diacylhydrazines (**3a**–**e**)

Benzhydrazide (**2**, 3.0 g, 0.02 mol) was suspended in dry diethyl ether (30 mL), then acid chloride (0.02 mol) dissolved in additional portion of dry diethyl ether (10 mL) was carefully added at room temperature. The reaction mixture was agitated at room temperature for about 30 min, then the solution of sodium carbonate (2.12 g, 0.02 mol) in water (15 mL) was added. The content of the flask was further agitated for 30 min, after which the white precipitate formed was filtered, washed with diethyl ether (20 mL), and air dried.

N′-Benzoyl-4-(bromomethyl)benzohydrazide (**3a**)

The product was obtained as white powder (5.73 g, 78%); m.p. 220–222 °C. 1H-NMR (400 MHz, DMSO): δ 4.77 (s, 2H), 7.53 (t, *J* = 8 Hz, 3H), 7.59 (d, *J* = 8 Hz, 2H), 7.92 (m, 4H), 10.52 (s, 1H), 10.53 (s, 1H); 13C-NMR (100 MHz, DMSO): δ 33.4, 127.4, 127.8, 128.5, 129.3, 131.8, 132.3, 132.5, 141.8, 165.4, 165.8. HRMS (ESI): *m*/*z* calcd for $C_{15}H_8BrN_2O_2$ + H^+: 333.0239, 335.0220; found 333.0234, 335.0219.

N′-(2-Bromoacetyl)benzohydrazide (**3b**)

The product was obtained as white powder (2.60 g, 46%); m.p. 152–154 °C. 1H-NMR (400 MHz, DMSO): δ 4.00 (s, 2H), 7.50 (t, *J* = 8 Hz, 2H), 7.59 (t, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 2H), 10.42 (s, 1H), 10.53 (s, 1H); 13C-NMR (100 MHz, DMSO): δ 27.1, 127.4, 128.5, 131.9, 132.2, 165.3, 165.4. HRMS (ESI): *m*/*z* calcd for $C_9H_9BrN_2O_2$ + H^+: 256.9926, 258.9906; found 256.9920, 258.9901.

N′-(3-Bromopropanoyl)benzohydrazide (**3c**)

The product was obtained as white powder (3.88 g, 65%); m.p. 154–156 °C. 1H-NMR (400 MHz, DMSO): δ 2.85 (t, *J* = 4Hz, 2H), 3.69 (t, *J* = 4 Hz, 2H), 7.49 (t, *J* = 4 Hz, 2H), 7.58 (m, 1H), 7.88 (d, *J* = 4 Hz, 2H), 10.06 (s, 1H), 10.42 (s, 1H); 13C-NMR (100 MHz, DMSO): δ 28.5, 36.6, 127.4, 128.4, 131.8, 132.3, 165.3, 168.5. HRMS (ESI): *m*/*z* calcd for $C_{10}H_{11}BrN_2O_2$ + H^+: 271.0082, 273.0063; found 271.0089, 273.0066.

N′-(4-Bromobutanoyl)benzohydrazide (**3d**)

The product was obtained as white powder (4.34 g, 69%); m.p. 115–117 °C. 1H-NMR (400 MHz, DMSO): δ 2.08 (q, *J* = 8 Hz, 2H), 2.36 (t, *J* = 8 Hz, 2H), 3.60 (t, *J* = 8 Hz, 2H), 7.51 (t, *J* = 8 Hz, 2H), 7.58 (m, 1H), 7.88 (d, *J* = 8 Hz, 2H), 9.93 (s, 1H), 10.30 (s, 1H); 13C-NMR (100 MHz, DMSO): δ 28.3, 31.6, 34.2, 38.9, 127.4, 128.4, 131.8, 132.4, 165.5, 170.5. HRMS (ESI): *m*/*z* calcd for $C_{11}H_{13}BrN_2O_2$ + H^+: 285.0239, 287.0219; found 285.0238, 287.0240.

N′-(5-Bromopentanoyl)benzohydrazide (**3e**)

The product was obtained as white powder (4.68 g, 71%); m.p. 133–134 °C. 1H-NMR (400 MHz, DMSO): δ 1.67 (m, 4H), 2.24 (t, *J* = 8 Hz, 2H), 3.57 (t, *J* = 8 Hz, 2H), 7.49 (t, *J* = 8 Hz, 3H), 7.90 (d, *J* = 8 Hz, 2H), 9.93 (s, 1H), 10.32 (s, 1H); 13C-NMR (100 MHz, DMSO): δ 23.7, 31.6, 32.3, 34.8, 127.8, 128.7, 130.4, 132.8, 165.7, 171.2. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}BrN_2O_2$ + H^+: 299.0395, 301.0376; found 299.0399, 301.0381.

3.2.3. Synthesis of Unsymmetrical 1,3,4-Oxadiazoles (**4a**–**e**)

N,N′-Diacylhydrazine (**3a**–**e**, 0.008 mol) was suspended in phosphorus oxychloride (26.0 mL, 0.28 mol).

Method A (conventional heating): The reaction mixture was kept in an oil bath at 70 °C for 1–8 h until the disappearance of the starting hydrazine derivative was fully completed, which was monitored by TLC (ethyl acetate/hexane; 2:1 *v*/*v*).

Method B (MW heating): The reaction mixture was placed in a microwave reactor under reflux condenser and the Dynamic method (100 W, 70 °C) was set in the device software. The progress of the reaction was monitored using TLC (ethyl acetate/hexane; 2:1 *v*/*v*).

Regardless of the method used, excess phosphorus oxychloride was evaporated using a rotary evaporator. Then, the residue was dissolved in ethyl acetate (40 mL) and poured into water (100 mL). The mixture was neutralized using sodium carbonate and extracted twice with diethyl ether (2 × 20 mL). Organic phase was dried over anhydrous magnesium sulfate, filtered, and rotary-evaporated.

2-(4-Bromomethyl)phenyl)-5-phenyl-1,3,4-oxadiazole (**4a**)

The product was obtained as white powder (2.52 g, 90%); m.p. 173–175 °C. 1H-NMR (400 MHz, DMSO): δ 4.76 (s, 2H), 7.53 (t, *J* = 8 Hz, 1H), 7.47 (d, *J* = 8 Hz, 3H), 7.60 (d,

J = 8 Hz, 1H), 7.95 (m, 5H); 13C-NMR (100 MHz, DMSO): δ 33.1, 126.2, 127.1, 128.8, 128.9, 129.1, 129.4, 129.5, 144.3, 165.6. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{11}BrN_2O + H^+$: 315.0133, 317.0114; found 315.0133, 317.0112.

2-(Bromomethyl)-5-phenyl-1,3,4-oxadiazole (**4b**)

The product was obtained as slightly yellow liquid (1.15 g, 60%). 1H-NMR (400 MHz, DMSO): δ 5.14 (s, 2H), 7.51 (t, *J* = 8 Hz, 1H), 7.65 (m, 3H), 8.04 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, DMSO): δ 16.2, 123.0, 126.8, 128.6, 129.6, 163.0, 165.1. HRMS (ESI): *m*/*z* calcd for $C_9H_7BrN_2O + H^+$: 238.9820, 240.9800; found 238.9832, 240.9812.

2-(2-Bromoethyl)-5-phenyl-1,3,4-oxadiazole (**4c**)

The product was obtained as slightly yellow liquid (0.69 g, 34%). 1H-NMR (400 MHz, DMSO): δ 3.57 (t, *J* = 8 Hz, 2H), 3.90 (t, *J* = 8 Hz, 2H), 7.61 (m, 3H), 8.01 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, DMSO): δ 28.5, 28.6, 117.5, 126.4, 129.4, 131.9, 164.1, 164.5. HRMS (ESI): *m*/*z* calcd for $C_{10}H_9BrN_2O + H^+$: 252.9977, 254.9957; found 252.9973, 254.9960.

2-(3-Bromopropyl)-5-phenyl-1,3,4-oxadiazole (**4d**)

The product was obtained as slightly yellow liquid (1.55 g, 73%). 1H-NMR (400 MHz, DMSO): δ 2.33 (q, *J* = 8 Hz, 2H), 3.09 (t, *J* = 8 Hz, 2H), 3.68 (t, *J* = 8 Hz, 2H), 7.60 (m, 3H), 8.00 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, DMSO): δ 23.5, 29.0, 33.6, 123.6, 126.5, 129.4, 131.9, 164.0, 165.8. HRMS (ESI): *m*/*z* calcd for $C_{11}H_{11}BrN_2O + H^+$: 267.0133, 269.0113; found 267.0120, 269.0111.

2-(4-Bromobutyl)-5-phenyl-1,3,4-oxadiazole (**4e**)

The product was obtained as slightly yellow liquid (1.39 g, 62%). 1H-NMR (400 MHz, DMSO): δ 1.22 (m, 2H), 1.93 (m, 2H), 2.99 (t, *J* = 8 Hz, 2H), 3.60 (t, *J* = 8 Hz, 2H), 7.62 (m, 3H), 7.99 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, DMSO): δ 23.8, 24.4, 31.4, 34.5, 123.6, 126.4, 129.4, 131.8, 163.9, 166.5. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{13}BrN_2O + H^+$: 281.0290, 283.0270; found 281.0284, 283.0265.

3.2.4. Synthesis of Diisopropyl Iminodiacetate (**6**)

Iminodiacetic acid (**5**) (15.0 g, 0.11 mol) was introduced into isopropanol (120 mL), and concentrated sulfuric acid (7.5 mL) was added there. The mixture was heated to reflux for 12 h. Excess isopropanol was then rotary-evaporated, and the residue was neutralized with aqueous sodium bicarbonate solution. Then, the resulting mixture was extracted twice with ethyl acetate (2 × 20 mL), and dried over anhydrous magnesium sulfate. The filtrate was evaporated to dryness, producing slightly yellow liquid.

Diisopropyl Iminodiacetate (**6**)

The product was obtained as slightly yellow liquid (12.41 g, 52%) [38]. 1H-NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 8 Hz, 12H), 3.85 (s, 4H), 5.11 (m, 2H); 13C-NMR (100 MHz, $CDCl_3$): δ 21.7, 48.6, 70.0, 167.6. HRMS (ESI): *m/z* calcd for $C_{10}H_{19}NO_4$ + H+: 218.1392; found 218.1403.

3.2.5. Synthesis of Unsymmetrical Ester Derivatives of 2-Alkyl-5-phenyl-1,3,4-oxadiazole (**7a**–**e**)

5-Phenyl-1,3,4-oxadiazole (**4a**–**e**, 0.004 mol), iminodiacetic acid ester (**6**, 0.004 mol), and sodium carbonate (4.24 g, 0.04 mol) were introduced into acetonitrile (40 mL). The mixture was heated at 60–80 °C for 12 h. Then, water (20 mL) was added there and extracted twice with ethyl acetate (2 × 25 mL). The organic extract was separated, dried over anhydrous magnesium sulfate, and rotary-evaporated. The crude products were purified by means of column chromatography with the use of ethyl acetate.

Diisopropyl 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzyl)azanediyl)diacetate (**7a**)

The product was obtained as slightly yellow liquid (1.69 g, 94%). 1H-NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 8 Hz, 12H), 3.53 (s, 4H), 4.01 (s, 2H), 5.07 (m, 2H), 7.54 (m, 3H), 7.60 (d, *J* = 8 Hz, 2H), 8.11 (d, *J* = 8 Hz, 2H), 8.16 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, $CDCl_3$): δ 21.9, 54.7, 57.4, 69.0, 123.0, 124.0, 126.9, 127.0, 129.0, 129.5, 131.6, 142.8, 164.4, 164.5, 170.6. HRMS (ESI): *m/z* calcd for $C_{25}H_{29}N_3O_5 + H^+$: 452.2185; found 452.2169.

Diisopropyl 2,2′-(((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)azanediyl)diacetate (**7b**)

The product was obtained as slightly yellow liquid (1.15 g, 76%). 1H-NMR (400 MHz, $CDCl_3$): δ 1.25 (d, *J* = 8 Hz, 12H), 3.69 (s, 4H), 4.31 (s, 2H), 5.06 (m, 2H), 7.52 (m, 3H), 8.06 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, $CDCl_3$): δ 21.8, 48.1, 55.0, 68.4, 123.8, 127.0, 128.9, 131.7, 163.5, 165.4, 170.0. HRMS (ESI): *m/z* calcd for $C_{19}H_{25}N_3O_5 + H^+$: 376.1873; found 376.1850.

Diisopropyl 2,2′-((2-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl)azanediyl)diacetate (**7c**)

The product was obtained as slightly yellow liquid (1.07 g, 69%). 1H-NMR (400 MHz, $CDCl_3$): δ 1.26 (d, *J* = 8 Hz, 12H), 3.43 (s, 4H), 3.53 (t, *J* = 8 Hz, 2H), 3.77 (t, *J* = 8 Hz, 2H), 5.07 (m, 2H), 7.53 (m, 3H), 8.05 (m, 2H); 13C-NMR (100 MHz, $CDCl_3$): δ 21.8, 26.1, 50.3, 60.3, 68.4, 126.8, 128.2, 129.0, 131.7, 163.9, 165.1, 171.1. HRMS (ESI): *m/z* calcd for $C_{20}H_{27}N_3O_5 + H^+$: 390.2029; found 390.2021.

Diisopropyl 2,2′-((3-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl)azanediyl)diacetate (**7d**)

The product was obtained as slightly yellow liquid (1.10 g, 68%). 1H-NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 4 Hz, 12H), 2.36 (m, 2H), 2.89 (t, *J* = 8 Hz, 2H), 3.04 (t, *J* = 8 Hz, 2H), 3.52 (s, 2H), 5.00 (m, 2H), 7.51 (m, 3H), 8.04 (d, *J* = 4 Hz, 2H); 13C-NMR (100 MHz, $CDCl_3$): δ 21.8, 22.9, 24.8, 43.6, 55.3, 68.0, 124.0, 126.7, 128.9, 131.4, 164.6, 166.8, 170.8. HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_3O_5 + H^+$: 404.2185; found 404.2095.

Diisopropyl 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)butyl)azanediyl)diacetate (**7e**)

The product was obtained as slightly yellow liquid (1.66 g, 80%). 1H-NMR (400 MHz, $CDCl_3$): δ 1.28 (d, *J* = 8 Hz, 12H), 1.94 (m, 2H), 2.05 (m, 2H), 2.99 (t, *J* = 8 Hz, 2H), 3.52 (s, 4H), 3.61 (t, *J* = 8 Hz, 2H), 5.08 (m, 2H), 7.52 (m, 3H), 8.05 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, $CDCl_3$): δ 21.7, 24.1, 25.2, 27.1, 53.5, 55.3, 68.1, 123.9, 126.8, 129.0, 131.6, 164.8, 166.7, 170.6. HRMS (ESI): *m/z* calcd for $C_{22}H_{31}N_3O_5 + H^+$: 418.2342; found 418.2339.

3.2.6. Synthesis of Unsymmetrical 2-Alkyl-5-phenyl-1,3,4-oxadiazole Derivatives Containing Bis(carboxymethyl)amino Group (**8a**–**e**)

The unsymmetrical ester derivatives of 2-alkyl-5-phenyl-1,3,4-oxadiazole (**7a**–**e**, 0.26 mmol) were introduced into the mixture of methanol (24 mL), water (6 mL), and NaOH (0.1 g, 2.6 mmol). The whole was heated at 50 °C for 30 min. Then, the mixture was neutralized with 1 M HCl and evaporated to dryness. The crude solid products were recrystallized from methanol.

2,2′-((4-(5-Phenyl-1,3,4-oxadiazol-2-yl)benzyl)azanediyl)diacetic Acid (**8a**)

The product was obtained as white powder (0.05 g, 51%). 1H-NMR (400 MHz, DMSO): δ 3.90 (s, 4H), 4.34 (s, 2H), 7.67 (t, *J* = 8 Hz, 3H), 7.77 (d, *J* = 8 Hz, 2H), 8.17 (m, 4H); 13C-NMR (100 MHz, DMSO): δ 53.7, 57.6, 123.3, 123.4, 126.7, 126.8, 129.4, 131.4, 132.1, 144.7, 163.8, 164.1, 167.7. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_3O_5 + H^+$: 368.1246; found 368.1241.

2,2′-(((5-Phenyl-1,3,4-oxadiazol-2-yl)methyl)azanediyl)diacetic Acid (**8b**)

The product was obtained as white powder (0.036 g, 47%). 1H-NMR (400 MHz, DMSO): δ 3.61 (s, 4H), 4.23 (s, 2H), 7.60 (t, *J* = 4 Hz, 3H), 7.96 (d, *J* = 4 Hz, 2H); 13C-NMR (100 MHz, DMSO): δ 47.5, 54.2, 123.5, 126.6, 129.5, 132.0, 163.8, 164.4, 171.9. HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_3O_5 + H^+$: 292.0934; found 292.0930.

2,2′-((2-(5-Phenyl-1,3,4-oxadiazol-2-yl)ethyl)azanediyl)diacetic Acid (**8c**)

The product was obtained as slightly yellow powder (0.033 g, 42%). 1H-NMR (400 MHz, DMSO): δ 3.53 (s, 4H), 3.60 (t, *J* = 8 Hz, 2H), 3.78 (t, *J* = 8 Hz, 2H), 7.61 (m, 3H), 7.91 (d, *J* = 8 Hz, 2H); 13C-NMR (100 MHz, DMSO): δ 25.8, 46.6, 58.0, 126.5, 127.9, 128.8, 132.0, 164.1, 165.2, 169.7. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}N_3O_5$ + H^+: 306.1090; found 306.1089.

2,2′-((3-(5-Phenyl-1,3,4-oxadiazol-2-yl)propyl)azanediyl)diacetic Acid (**8d**)

The product was obtained as slightly yellow powder (0.035 g, 44%). 1H-NMR (400 MHz, DMSO): δ 2.11 (m, 2H), 2.25 (m, 2H), 2.98 (m, 2H), 4.09 (s, 4H), 7.43 (m, 3H), 7.83 (d, *J* = 4 Hz, 2H); 13C-NMR (100 MHz, DMSO): δ 20.8, 22.1, 54.3, 54.7, 123.6, 129.6, 129.6, 132.0, 164.1, 166.0, 168.2. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}N_3O_5$ + H^+: 320.1246; found 320.1233.

2,2′-((4-(5-Phenyl-1,3,4-oxadiazol-2-yl)butyl)azanediyl)diacetic Acid (**8e**)

The product was obtained as slightly yellow powder (0.036 g, 41%). 1H-NMR (400 MHz, DMSO): δ 1.93 (m, 4H), 2.99 (t, *J* = 4Hz, 2H), 3.48 (s, 4H), 3.71 (t, *J* = 4 Hz, 2H), 7.50 (m, 3H), 7.92 (m, 2H); 13C-NMR (100 MHz, DMSO): δ 23.2, 23.9, 31.2, 50.4, 54.7, 123.5, 126.4, 129.4, 131.8, 163.9, 165.5, 171.3. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}N_3O_5$ + H^+: 334.1403; found 334.1401.

4. Conclusions

In summary, unsymmetrical *N*,*N*′-diacylhydrazines containing bromomethylphenyl and bromoalkyl groups appeared to be useful intermediates in the synthesis of 5-phenyl-1,3,4-oxadiazoles bearing at position 2 benzyl or alkyl substituents, both equipped with bis(carboxymethyl)amino functionality. The cyclization of *N*,*N*′-diacylhydrazines to 1,3,4-oxadiazoles proceeded smoothly with phosphoryl chloride $POCl_3$ or phosphorus pentoxide P_2O_5 under the action of microwave irradiation. However, the substitution of the terminal bromine in molecules of 2-(4-bromophenyl)-5-phenyl-1,3,4-oxadiazole and 2-bromoalkyl-5-phenyl-1,3,4-oxadiazoles required the use of a more reactive iminodiacetic acid derivative, namely diisopropyl iminodiacetate. The esters formed were effectively cleaved via basic hydrolysis in a water–methanol solution, yielding the desired 1,3,4-oxadiazole hybrids. In the very near future, we plan to increase the scale of the synthesis of the 5-phenyl-1,3,4-oxadiazole derivatives and study their biological activity. The final products obtained may constitute a new group of heterocyclic ligands with potential application in various fields such as medicine, pharmacy, and agriculture.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/app132212427/s1: Figure S1: ^{1}H NMR spectra (400 MHz, dmso) of benzhydrazide (**2**); Figure S2: ^{13}C NMR spectra (100 MHz, dmso) of benzhydrazide (**2a**); Figure S3: ^{1}H NMR spectra (400 MHz, dmso) of *N*′-benzoyl-4-(bromomethyl)benzohydrazide (**3a**); Figure S4: ^{13}C NMR spectra (100 MHz, dmso) of *N*′-benzoyl-4-(bromomethyl)benzohydrazide (**3a**); Figure S5: ^{1}H NMR spectra (400 MHz, dmso) of *N*′-(2-bromoacetyl)benzohydrazide (**3b**); Figure S6: ^{13}C NMR spectra (100 MHz, dmso) of *N*′-(2-bromoacetyl)benzohydrazide (**3b**); Figure S7**:** ^{1}H NMR spectra (400 MHz, dmso) of *N*′-(3-bromopropanoyl)benzohydrazide (**3c**); Figure S8: ^{13}C NMR spectra (100 MHz, dmso) of *N*′-(3-bromopropanoyl)benzohydrazide (**3c**); Figure S9: ^{1}H NMR spectra (400 MHz, dmso) of *N*′-(4-bromobutanoyl)benzohydrazide (**3d**); Figure S10: ^{13}C NMR spectra (100 MHz, dmso) of *N*′-(4-bromobutanoyl)benzohydrazide (**3d**); Figure S11: ^{1}H NMR spectra (400 MHz, dmso) of *N*′-(5-bromopentanoyl)benzohydrazide (**3e**); Figure S12: ^{13}C NMR spectra (100 MHz, dmso) of *N*′-(5-bromopentanoyl)benzohydrazide (**3e**); Figure S13: ^{1}H NMR spectra (400 MHz, dmso) of 2-(4-bromomethyl)phenyl)-5-phenyl-1,3,4-oxadiazole (**4a**); Figure S14: ^{13}C NMR spectra (100 MHz, dmso) of 2-(4-bromomethyl)phenyl)-5-phenyl-1,3,4-oxadiazole (**4a**); Figure S15: ^{1}H NMR spectra (400 MHz, dmso) of 2-(bromomethyl)-5-phenyl-1,3,4-oxadiazole (**4b**); Figure S16; ^{13}C NMR spectra (100 MHz, dmso) of 2-(bromomethyl)-5-phenyl-1,3,4-oxadiazole (**4b**); Figure S17: ^{1}H NMR spectra (400 MHz, dmso) of 2-(2-bromoethyl)-5-phenyl-1,3,4-oxadiazole (**4c**); Figure S18: ^{13}C NMR spectra (100 MHz, dmso) of 2-(2-bromoethyl)-5-phenyl-1,3,4-oxadiazole (**4c**); Figure S19: ^{1}H NMR spectra (400 MHz, dmso) of 2-(3-bromopropyl)-5-phenyl-1,3,4-oxadiazole (**4d**); Figure S20: ^{13}C NMR spectra (100 MHz,

dmso) of 2-(3-bromopropyl)-5-phenyl-1,3,4-oxadiazole (**4d**); Figure S21: ^{1}H NMR spectra (400 MHz, dmso) of 2-(4-bromobutyl)-5-phenyl-1,3,4-oxadiazole (**4e**); Figure S22: ^{13}C NMR spectra (100 MHz, dmso) of 2-(4-bromobutyl)-5-phenyl-1,3,4-oxadiazole (**4e**); Figure S23: ^{1}H NMR spectra (400 MHz, CDCl3) of diisopropyl iminodiacetate (**6**); Figure S24: ^{13}C NMR spectra (100 MHz, CDCl3) of diisopropyl iminodiacetate (**6**); Figure S25: ^{1}H NMR spectra (400 MHz, $CDCl_3$) of diisopropyl 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzyl)azanediyl)diacetate (**7a**); Figure S26: ^{13}C NMR spectra (100 MHz, CDCl3) of diisopropyl 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzyl)azanediyl)diacetate (**7a**); Figure S27: ^{1}H NMR spectra (400 MHz, $CDCl_3$) of diisopropyl 2,2′-(((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)azanediyl)diacetate (**7b**); Figure S28: ^{13}C NMR spectra (100 MHz, CDCl3) of diisopropyl 2,2′-(((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)azanediyl)diacetate (**7b**); Figure S29: ^{1}H NMR spectra (400 MHz, $CDCl_3$) of diisopropyl 2,2′-((2-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl)azanediyl)diacetate (**7c**); Figure S30: ^{13}C NMR spectra (100 MHz, CDCl3) of diisopropyl 2,2′-((3-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl)azanediyl)diacetate (**7d**); Figure S31: ^{1}H NMR spectra (400 MHz, CDCl3) of diisopropyl 2,2′-((3-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl)azanediyl)diacetate (**7d**); Figure S32: ^{13}C NMR spectra (100 MHz, CDCl3) of diisopropyl 2,2′-((3-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl)azanediyl)diacetate (**7d**); Figure S33: ^{1}H NMR spectra (400 MHz, CDCl3) of diisopropyl 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)butyl)azanediyl)diacetate (**7e**); Figure S34: ^{13}C NMR spectra (100 MHz, CDCl3) of diisopropyl 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)butyl)azanediyl)diacetate (**7e**); Figure S35: ^{1}H NMR spectra (400 MHz, dmso) of 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzyl)azanediyl)diacetic acid (**8a**); Figure S36: ^{13}C NMR spectra (100 MHz, dmso) of 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzyl)azanediyl)diacetic acid (**8a**); Figure S37: ^{1}H NMR spectra (400 MHz, dmso) of 2,2′-(((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)azanediyl)diacetic acid (**8b**); Figure S38: ^{13}C NMR spectra (100 MHz, dmso) of 2,2′-(((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)azanediyl)diacetic acid (**8b**); Figure S39: ^{1}H NMR spectra (400 MHz, dmso) of 2,2′-((2-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl)azanediyl)diacetic acid (**8c**); Figure S40: ^{13}C NMR spectra (100 MHz, dmso) of 2,2′-((2-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl)azanediyl)diacetic acid (**8c**); Figure S41: ^{1}H NMR spectra (400 MHz, dmso) of 2,2′-((3-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl)azanediyl)diacetic acid (**8d**); Figure S42: ^{13}C NMR spectra (100 MHz, dmso) of 2,2′-((3-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl)azanediyl)diacetic acid (**8d**); Figure S43: ^{1}H NMR spectra (400 MHz, dmso) of 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)butyl)azanediyl)diacetic acid (**8e**); Figure S44: ^{13}C NMR spectra (100 MHz, dmso) of 2,2′-((4-(5-phenyl-1,3,4-oxadiazol-2-yl)butyl)azanediyl)diacetic acid (**8e**).

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