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N-PROTECTED N^2-ETHOXYMETHYLENE PHENYLGLYCINE HYDRAZIDES AS PRECURSORS OF 1,3,4-OXADIAZOLE DERIVATIVES

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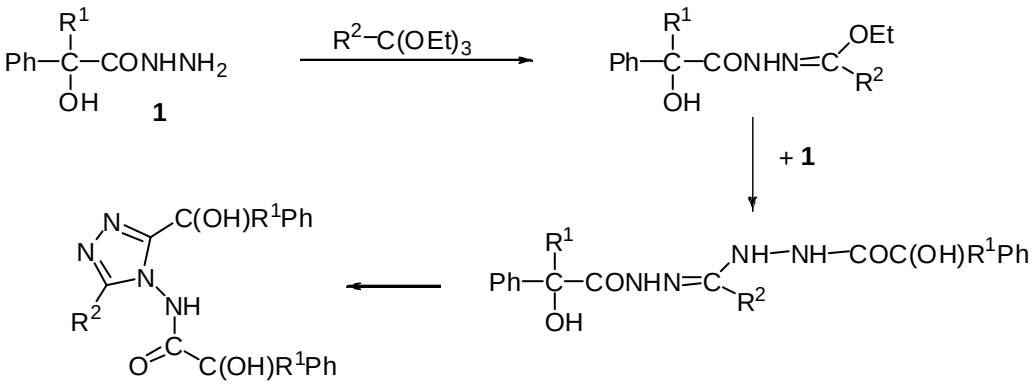
Abstract – New derivatives of N^2-ethoxymethylene phenylglycine hydrazide protected at the amino group by acetyl and *tert*-butoxycarbonyl were synthesized with reactions of *N*-protected phenylglycine hydrazides and triethyl orthoesters. They underwent cyclization to the corresponding *N*-protected 2-aminomethyl-1,3,4-oxadiazoles in the presence of glacial acetic acid.

INTRODUCTION

1,3,4-Oxadiazoles belong to the group of five-membered, non-naturally occurring aromatic heterocycles.[1] These compounds were first mentioned in the literature during the late fifties.[2,3] They have attracted the attention of many scientists due to a broad spectrum of biological activity. 1,3,4-Oxadiazoles display antibacterial, anticonvulsant, antidepressive, anticancer, and antifungal activities, which makes them potentially useful agents in medicine and agriculture.[4-8] Conjugated macrocyclic arrangements based on the 1,3,4-oxadiazole fragment exhibit interesting electron-transfer or luminescent properties and are used in organic light-emitting diodes (OLED), optical brighteners, and laser dyes.[9-11]

The most popular method to obtain 1,3,4-oxadiazoles is the cyclodehydration of diacylhydrazines in the presence of dehydrating agents such as: polyphosphoric acid,[12] phosphorus oxychloride,[13] thionyl chloride,[14] or boron trifluoride diethyl etherate.[15] The starting diacylhydrazines, contain in their structure all the atoms essential for the construction of such a ring, and are usually prepared in reactions of acid hydrazides with synthons, which introduce another carbon atom to the structure. On the other hand, hydrazides could also react with aromatic aldehydes[16] or orthoesters[17,18] to yield the desired 1,3,4-oxadiazoles. Our earlier studies on the synthesis of 4-acylamino-1,2,4-triazole derivatives in the reaction of α-hydroxyacid hydrazides with triethyl orthoesters showed that the reactions proceed through

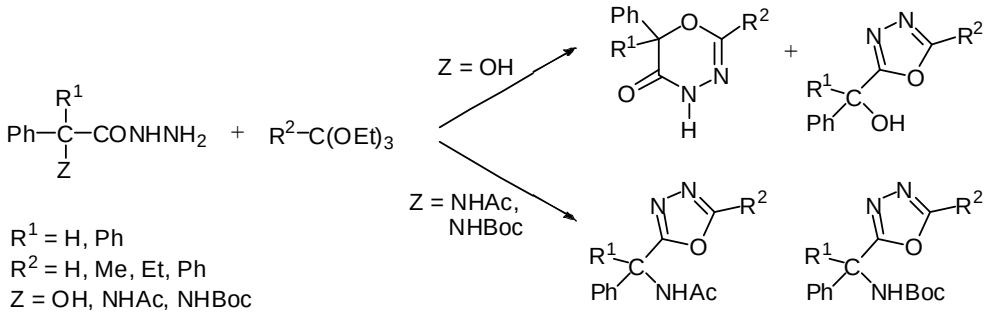
stable acyclic intermediate, a derivative of N^2-ethoxymethylene α-hydroxyacid hydrazide (Scheme 1).[19] These compounds contain an imine carbon atom that is susceptible to attack from nucleophiles, which react with another molecule of acid hydrazide to yield the longer chain, the acyclic *N,N'*-bis(1-hydroxy-1-phenylmethane-carbonylamino)formamidine. This undergoes further cyclization to the desired 1,2,4-triazole in acidic medium at elevated temperature.



R^1 = H, Ph
R^2 = H, Me, Et

Scheme 1

Some selected α-hydroxyacid hydrazides and triethyl orthoesters were applied in the one-step synthesis of other heterocyclic arrangements: five-membered 2-hydroxymethyl-1,3,4-oxadiazoles and six-membered 1,3,4-oxadiazin-5(*6H*)-ones (Scheme 2). The reactions were held in the presence of glacial acetic acid to give a mixture of these two cyclic compounds. The yields of five-membered 1,3,4-oxadiazoles depend on the type of substituent R^2 attached to the orthoester. The more bulky the substituent R^2 is, the higher the oxadiazole yields. The reversed trend was observed in the case of 1,3,4-oxadiazin-5(*6H*)-one derivatives. The formation of the latter six-membered compounds resulted from the presence of a highly reactive hydroxy group in hydrazide.[20]



R^1 = H, Ph
R^2 = H, Me, Et, Ph
Z = OH, NHAc, NHBoc

Scheme 2

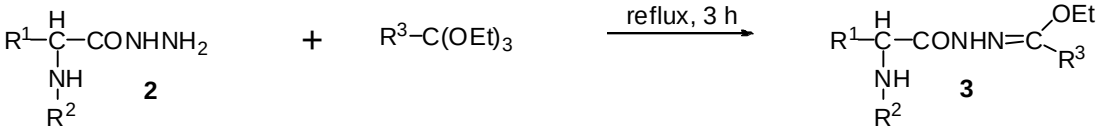
The reduction of the nucleophilic group situated at the α-position by introducing a protective grouprevents the formation of the six-membered compound and increases the yield of 1,3,4-oxadiazole.

Consequently, the derivatives of 2-aminomethyl-1,3,4-oxadiazoles were the only products of the reactions of *N*-protected phenylglycine hydrazides and triethyl orthoesters (Scheme 2).[21]

According to our assumed reaction mechanism, the intermediate compound N^2-ethoxymethylene hydrazide should play the key role in the building of the heterocyclic products mentioned above. We decided to synthesize such N^2-ethoxymethylene acid hydrazides protected at the highly reactive amino group and find proper conditions to obtain the desired 2-aminomethyl-1,3,4-oxadiazoles.

RESULTS AND DISCUSSION

The four enantiomeric phenylglycine hydrazides **2** substituted at the amino group with acetyl (Ac) and *tert*-butoxycarbonyl group (Boc) were used as starting materials. They were prepared according to a short procedure described in the literature from two enantiomers of phenylglycine and two typical protective agents: acetic anhydride and di-*tert*-butyl pyrocarbonate.[21] The commercially available triethyl orthoesters (R^3 = H, Me, Et, Ph), play the dual role of the synthon introducing the methylene carbon atom and the solvent, were applied in the synthesis. The hydrazides and orthoesters were heated to obtain a series of *N*-protected N^2-ethoxymethylene phenylglycine hydrazides **3a-f** (Scheme 3).



	R^1	R^2
2a	Ph (*L*)	Ac
2b	Ph (*D*)	Ac
2c	Ph (*L*)	Boc
2d	Ph (*D*)	Boc

Scheme 3

The best results were obtained when the reactions were conducted in excess orthoester, although in some cases there were problems with separation of products from the post-reaction mixture. The yields of **3a-f** fairly vary from 51 to 90% (Table 1) and depend on the kind of substituent R^3 from the orthoester molecule. The best result was obtained for the *N*-Boc-protected N^2-ethoxymethylene phenylglycine hydrazide with the imine carbon atom substituted with the phenyl group (**3f**, entries 11 and12), which seems to be quite reasonable due to the presence of the conjugated system. The rest of the iminoesters with electron-donating substituents resulted in slightly lower yields. The optical rotations of four series of *N*-protected N^2-ethoxymethylene phenylglycine hydrazides **3** obtained from enantiomeric substrates **2** were investigated and showed that they exist as racemic mixtures. These observations were somewhat unexpected because the stereogenic carbon atom situated at the opposite part of the molecule was not involved in the formation of iminoester **3**. It is possible that triethyl orthoester, a polar solvent and reagent,

could have been responsible for this phenomenon. We decided to decrease the amount of orthoester to the stoichiometric level and conduct the reaction in the presence of xylene, which is a nonpolar solvent with a boiling point similar to orthoester. Unfortunately, even in this case the racemization occurred, proving that an equimolar amount is sufficient for the reaction.

Table 1. Synthesis of *N*-protected phenylglycine N^2-ethoxymethylenehydrazides **3**[a]

Entry	Compound	R^1	R^2	R^3	Yield %	$[\alpha]_D^{20}$
1	**3a**	Ph(*L*)	Ac	H	65	+ 0.5
2		Ph(*D*)	Ac	H	61	- 0.2
3	**3b**	Ph(*L*)	Ac	Et	70	+ 0.1
4		Ph(*D*)	Ac	Et	74	0.0
5	**3c**	Ph(*L*)	Boc	H	51	+ 1.5
6		Ph(*D*)	Boc	H	55	- 0.2
7	**3d**	Ph(*L*)	Boc	Me	66	+ 0.5
8		Ph(*D*)	Boc	Me	64	- 1.3
9	**3e**	Ph(*L*)	Boc	Et	74	+ 0.7
10		Ph(*D*)	Boc	Et	78	- 0.8
11	**3f**	Ph(*L*)	Boc	Ph	88	+ 1.0
12		Ph(*D*)	Boc	Ph	90	- 1.0

[a] The reactions were conducted in the excess of orthoester, reflux, 3 h.

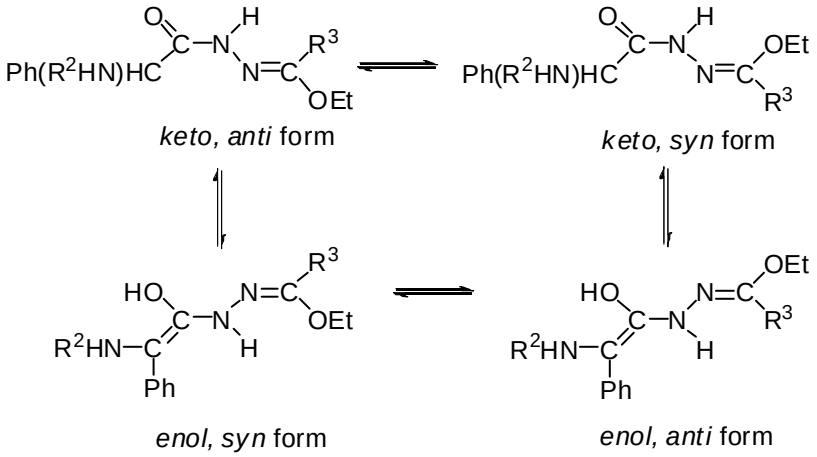
The new compounds were characterised by elemental analysis, IR, NMR spectroscopy, and mass spectrometry. According to ^{1}H-NMR analysis, the *N*-protected N^2-ethoxymethylene phenylglycine hydrazides **3a-f** exist in DMSO solution as a mixture of four different forms, due to the quadruple number of peaks for each group of protons (Table 2). Multiplied signals coalesced upon heating the solution to 100°C. The most characteristic signals in the ^{1}H-NMR spectra come from protons of the ethoxy group that were introduced to molecule **3** by the orthoester, and appears as a triplet (-CH_3) at ca. 1.20 ppm and a quartet (-CH_2-) from 3.71 to 4.21ppm. The doublets of proton of the parent phenylglycine fragment appear in the broad range from 5.18 to 6.22 ppm. There are also large differences in the chemical shifts of the proton adjacent to the protected amino group. If N^2-ethoxymethylene phenylglycine hydrazide is substituted with an acetyl group (**3a**, **3b**), the proton doublet appears at about 8.40-8.63 ppm. For the *tert*-butoxycarbonyl group (**3c-f**), it appears in the aromatic range (7.30-7.56 ppm). In the ^{13}C-NMR spectra, the characteristic methylene carbon atom are observed at ca.165 ppm. Two other typical signals

of the ethoxy group that was introduced to the N^2-ethoxymethylene phenylglycine hydrazide moiety, appear at 15 ppm (-CH_3) and 62-67 ppm (-OCH_2-). Thus, the formation of the four different structures is the result of both structural and stereo isomerisms.

Table 2. Data of ^{1}H-NMR spectra of compounds **3a-f**

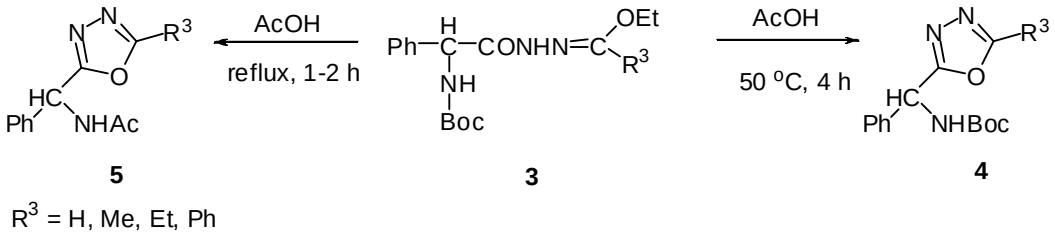
Compound	Chemical shift, δ, ppm (DMSO-d_6)						
	$OCH_2\underline{CH_3}$ t	$O\underline{CH_2}CH_3$ q	R^3	H d	R^2-NH d	CONH s	other signals
3a	1.18 1.22	4.01 4.18	6.78 6.86 7.94 8.26	5.41 5.78 6.05 6.22	8.40 8.42 8.58 8.83	10.05 10.64	1.85 (CH_3CO) 1.88 (CH_3CO) 7.26-7.34 (Ph)
3b	1.18 1.22	4.02 4.16	0.96 ($CH_2\underline{CH_3}$) 1.05 ($CH_2\underline{CH_3}$) 2.24 ($\underline{CH_2}CH_3$) 2.36 ($\underline{CH_2}CH_3$)	5.60 5.78 6.12 6.20	8.42 8.63	9.80 10.16 10.35 10.45	1.86 (CH_3CO) 1.91 (CH_3CO) 7.20-7.46 (Ph)
3c	1.21 1.24 1.30	3.71 4.06 4.21	6.40 6.61 8.05	5.84 5.94 6.10	7.40-7.52 (m)	8.68 8.95	1.40 (*t*-Bu) 1.42 (*t*-Bu) 7.24-7.36 (Ph)
3d	1.21 1.24	4.02 4.12	1.99 2.08	5.85 5.97 6.12	7.40-7.56 (m)	8.53 8.76 8.88	1.38 (*t*-Bu) 1.41 (*t*-Bu) 7.20-7.36 (Ph)
3e	1.25 1.27	3.98 4.13	1.03 ($CH_2\underline{CH_3}$) 1.14 ($CH_2\underline{CH_3}$) 2.32 ($\underline{CH_2}CH_3$) 2.38 ($\underline{CH_2}CH_3$)	5.76 5.88 5.94 6.07	7.30-7.55 (m)	8.35 8.78 8.85 8.88	1.38 (*t*-Bu) 1.41 (*t*-Bu) 7.22-7.34 (Ph)
3f	1.04 1.19 1.21 1.28	3.90 3.96 3.98 4.20	7.38 (1H, t, J=6.9 Hz, H-4”); 7.44-7.52 (m, H-3”, H-5”) 7.60 (2H, d, J =6.9 Hz, H-2”,6”)	5.18 5.59 5.90 6.04	7.44-7.52 (m)	9.75 10.26 10.67 10.76	1.36 (*t*-Bu) 1.38 (*t*-Bu) 7.26-7.34 (Ph)

In our early work on the synthesis of N^2-ethoxymethylene benzilic acid hydrazides we found that they exist as a mixture of only two geometric *syn* and *anti* isomers relative to the N=C double bond.[19] Similar observations were also noted for different heterocyclic hydrazones derived from acidic hydrazides and carbonyl compounds.[22,23] However, the presence of the second group of peaks is caused by tautomerism. Phenylglycine derivatives in polar solvents (orthoester, DMSO) exist in two ketone and enol forms, which changes the stereochemistry of the N^2-ethoxymethylene hydrazides. They form four different stereoisomers that are in dynamic equilibrium and exhibit nonequivalent spectra (Scheme 4). The optical activity at the stereogenic carbon atom in the two enol structures (*enol, syn* form, *enol, anti* form) disappears, and the racemisation is observed.



Scheme 4

The new *N*-Boc protected N^2-ethoxymethylene phenylglycine hydrazides (**3c-f**) were the focus of our study on the cyclization to 1,3,4-oxadiazole derivatives. The initial trials involving the heating of *N*-Boc protected N^2-ethoxymethylene phenylglycine hydrazides (**3c-f**) in inert solvents such as: benzene, toluene, and xylene were unsuccessful. The cyclization of the compounds proceeded at 50 °C in glacial acetic acid (AcOH) yielding the appropriate 2-(1-*N*-*tert*-butoxycarbonylamino-1-phenylmethyl)-1,3,4-oxadiazoles (**4a-d**). When the mixture of the acyclic N^2-ethoxymethylene hydrazide (**3c-f**) in AcOH was refluxed, the cyclization was accompanied by the exchange of the protection group, which led to the derivatives of 2-(1-*N*-acetylamino-1-phenylmethyl)-1,3,4-oxadiazole (**5a-d**).



Scheme 5

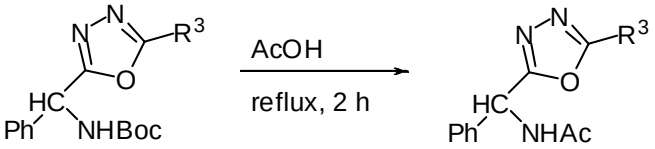
The yields of two of the series are high, from 75 to 92% (Table 3). Similar to the starting N^2-ethoxymethylene phenylglycine hydrazides, the highest values were observed for 1,3,4-oxadiazoles substituted with a phenyl group at position five (**4d** and **5d**).

Table 3. Synthesis of *N*-Boc and *N*-Ac protected 1,3,4-oxadiazole derivatives **4a-d**, **5a-d**[a]

Compound	R^3	Yield %
4a	H	75
4b	Me	81
4c	Et	85
4d	Ph	92
5a	H	94
5b	Me	95
5c	Et	95
5d	Ph	98

[a] The reactions were conducted in glacial AcOH; **4a-d** at 50 °C for 4 h; **5a-d** at reflux for 1-2 h.

In contrast, slightly lower yields were obtained from compounds possessing electron-donating groups such as alkyl moieties. They decrease the electrophilicity of the imine carbon atom in **3** and reduce its reactivity in the internal cyclization reaction.



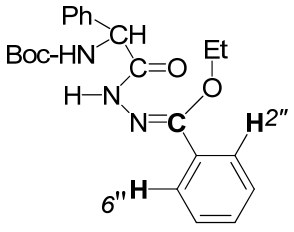
4 **5**

	R^3	Yield %
5b	Me	82
5d	Ph	95

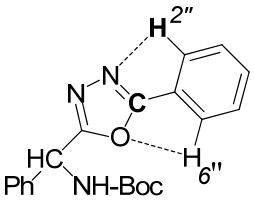
Scheme 6

We investigated whether *N*-Boc substituted 1,3,4-oxadiazoles could be directly transformed into their *N*-Ac counterparts (Scheme 6). Two 2-(1-*N*-Boc-amino-1-phenylmethyl)-1,3,4-oxadiazoles possessing methyl (**4b**) and phenyl (**4d**) at R^3 were refluxed in glacial acetic acid. The progress of the reaction was controlled using TLC analysis. The protecting group was rapidly exchanged to produce the appropriate 2-(1-*N*-Ac-amino-1-phenylmethyl)-1,3,4-oxadiazoles (**5b** and **5d**) in high yields (82-95%).

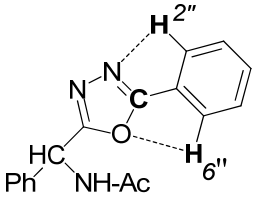
It is worth focusing on the structures of two protected 2-(1-amino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazoles: **4d** (-NHBoc) and **5d** (-NHAc) (Scheme 7), which can be obtained from the corresponding N^2-ethoxymethylene-2-(*N*-Boc-amino)-2-phenylacethydrazide **3f**. Observations show that cyclization makes no measureable changes in the methylene carbon atom shifts. Paraschivescu *et al.* made similar observations of the synthesis on non-symmetrically 2,5-disubstituted 1,3,4-oxadiazoles containing a benzo[*b*]thiophene moiety.[24] They suggest that such insignificant changes in the chemical shifts of the 1,3,4-oxadiazole carbon atoms in ^{13}C-NMR spectra prove the lack of conjugation between the oxadiazole ring and the aryl moiety. However, that conclusion is questionable if the ^{1}H-NMR spectra of the derivatives **4d** and **5d** are considered. The two protons H-2" and H-6" of the phenyl group substituted at position five of the 1,3,4-oxadiazole ring are shifted to lower fields, which arise from their proximity to the ring's nitrogen and oxygen atoms.



3f



4d



5d

^{1}H-NMR: δ	H-2", 6"	7.60 ppm	7.95 ppm	7.95 ppm
^{13}C-NMR: δ	C5=N4	166.69 ppm	164.33 ppm	164.37 ppm

Scheme 7

Results indicate that both 1,3,4-oxadiazole and the phenyl rings lie untwisted in the same plane and are conjugated. The X-ray analysis of **5d** revealed that even in the solid state the rings are nearly coplanar. Such an interaction leads to the exceptional stability in the deprotection of *N*-protected 2-(1-aminomethyl)-1,3,4-oxadiazoles proceeding in acidic media.[21]

CONCLUSIONS

New derivatives of N^2-ethoxymethylene phenylglycine hydrazide, obtained in the reactions of *N*-protected phenylglycine hydrazides and triethyl orthoesters, are valuable reagents for the preparation of non-symmetrically substituted *N*-protected 2-aminomethyl-1,3,4-oxadiazoles. The cyclization of the N^2-ethoxymethylene phenylglycine hydrazides carried out in glacial acetic acid appears to be an efficient, rapid, and easy way to obtain five-membered 1,3,4-oxadiazoles. The presented protocol may be especially useful in the synthesis of macrocyclic systems based on the easy-to-bind 2-aminomethyl-1,3,4-oxadiazole moiety.

EXPERIMENTAL

Melting points were measured using an APA II melting point apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-2102 spectrophotometer. Elemental analyses were performed with a VarioEL analyser in PAN Zabrze. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Inova 300 spectrometer in DMSO solution using TMS as the internal standard. Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck) thin-layer chromatography plates using benzene-AcOEt (1:5 v/v) as the mobile phase. Optical rotations were measured on a Perkin Elmer Polarimeter 141 in $CHCl_3$ solutions at approximately 1% concentrations (D line of sodium light, room temperature). IR spectra were recorded between 3800-600 cm^{-1} on a Zeiss Specord 80 spectrometer in MeCN solutions. Mass spectra were obtained on a Waters HPLC/MS system using the EI technique (70 eV).

Synthesis of α-*N*-protected phenylglycine hydrazides (2). The appropriate *α-N*-protected phenylglycine hydrazides were obtained according to a procedure described in the literature from the two enantiomers of phenylglycine.

L-(+)-*N*-Ac-phenylglycine hydrazid*e* (**2a**).[21]

Yield: 85%, mp 210-212 °C, $[\alpha]_D^{20}$ +95.2 (MeOH, C = 1%), IR (MeCN) ν/cm^{-1}: 3645, 3540, 3020, 1690, 1640, 1230, 770, 665.

D-(-)-*N*-Ac-phenylglycine hydrazide (**2b**).[21]

Yield: 90%, mp 196-198 °C, $[\alpha]_D^{20}$ –93.6 (MeOH, C = 1%).

L-(+)-*N*-Boc-phenylglycine hydrazide (**2c**).[21]

Yield: 66%, mp 105-107 °C, $[\alpha]_D^{20}$ +105.3 ($CHCl_3$, C = 1%), IR (MeCN) ν/cm^{-1}: 3650, 3540, 3360, 2980, 2940, 1720, 1690, 1630, 1250, 1170, 710.

D-(-)-*N*-Boc-phenylglycine hydrazide (**2d**).[21]

Yield: 73%, mp 118-121 °C, $[\alpha]_D^{20}$ -101.7 ($CHCl_3$, C = 1%).

General procedure for the preparation of *N*-protected N^2-ethoxymethylene phenylglycine hydrazides (3a-f). The starting *α-N*-protected phenylglycine hydrazide 2 (0.01 mol) was added to a mixture of the appropriate triethyl orthoester (0.05 mol) and kept under reflux for about 3 h (TLC). After cooling, the excessive orthoester was evaporated under reduced pressure. The crude oils were triturated with Et_2O and then purified by crystallization from benzene-hexane mixtures.

N^2-Ethoxymethylene-2-(*N*-Ac-amino)-2-phenylacethydrazide (**3a**, Entries 1 and 2).

This compound was obtained as a white solid in 63% yield, mp 124-125 °C, R_f 0.10 (benzene-AcOEt, 1:5 v/v). (Anal. Calcd for $C_{13}H_{17}N_3O_3$: C, 59.29; H, 6.52; N, 15.95. Found: C, 59.41; H, 6.59; N, 16.03%). UV λ_{max} (MeOH): 202 nm ($\varepsilon \cdot 10^{-3}$ 13.01 $cm^{-1}M^{-1}$), 227 (9.15). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.78,

23.04, 56.16, 63.11, 127.85, 128.02, 128.95, 139.35, 155.68, 166.39, 169.73. MS (EI, 70 eV) *m/z* (%): 217 (10), 175 (15), 149 (24), 132 (11), 106 (100), 105 (36), 104 (52), 91 (18), 79 (21), 77(42), 71 (19), 60 (25), 57 (18). IR (MeCN) ν/cm^{-1}: 3420, 3380, 3015, 1665, 1520, 1240, 1080, 710.

N^2-Ethoxypropylene-2-(*N*-Ac-amino)-2-phenylacethydrazide (**3b**, Entries 3 and 4).

This compound was obtained as a white solid in 72% yield, mp 177-178 °C, R_f 0.15 (benzene-AcOEt, 1:5 v/v). (Anal. Calcd for $C_{15}H_{21}N_3O_3$: C, 68.42; H, 7.28; N, 14.41. Found: C, 68.59; H, 7.32; N, 14.50%). UV λ_{max} (MeOH): 203 nm ($\varepsilon \cdot 10^{-3}$ 15.11 cm^{-1}M^{-1}), 228 (8.23). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 9.55, 14.07, 21.67, 22.40, 55.05, 61.81, 127.06, 127.44, 128.21, 139.00, 165.49, 168.52, 169.01. MS (EI, 70 eV) *m/z* (%): 245 (12), 202 (23), 175 (10), 149 (28), 143 (19), 132 (16), 115 (12), 106 (100), 105 (24), 104 (71), 94 (48), 91 (32), 89 (12), 79 (26), 77 (45), 57 (41). IR (MeCN) ν/cm^{-1}: 3420, 3380, 3010, 1660, 1510, 1240, 1080, 700.

N^2-Ethoxymethylene-2-(*N*-Boc-amino)-2-phenylacethydrazide (**3c**, Entries 5 and 6).

This compound was obtained as a white solid in 53% yield, mp 143-144 °C, R_f 0.50 (benzene-AcOEt, 1:5 v/v). (Anal. Calcd for $C_{16}H_{23}N_3O_4$: C, 59.80; H, 7.10; N, 13.13. Found: C, 59.71; H, 7.15; N, 13.05%). UV λ_{max} (MeOH): 202 nm ($\varepsilon \cdot 10^{-3}$ 13.44 cm^{-1}M^{-1}), 233 (11.64). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.10, 28.16, 58.86, 62.48, 78.42, 127.22, 128.21, 128.29, 138.45, 154.97, 161.08, 171.14. MS (EI, 70 eV) *m/z* (%): 206 (21), 151 (12), 132 (10), 115 (15), 106 (100), 104 (18), 87 (11), 79 (14), 77 (13), 59 (15), 57 (82). IR (MeCN) ν/cm^{-1}: 3645, 3548, 3362, 2995, 2954, 1710, 1634, 1317, 1243, 1168, 1084, 895.

N^2-Ethoxyethylene-2-(*N*-Boc-amino)-2-phenylacethydrazide (**3d**, Entries 7 and 8).

This compound was obtained as a white solid in 65% yield, mp 119-121 °C, R_f 0.52 (benzene-AcOEt, 1:5 v/v). (Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 61.12; H, 7.41; N, 12.53. Found: C, 61.21; H, 7.39; N, 12.56%). UV λ_{max} (MeOH): 202 nm ($\varepsilon \cdot 10^{-3}$ 14.51cm^{-1}M^{-1}), 230 (9.43). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.61, 15.78, 28.68, 57.11, 62.42, 78.90, 127.16, 128.06, 128.33, 139.19, 155.01, 165.55, 171.00. MS (EI, 70 eV) *m/z* (%): 206 (10), 151 (12), 150 (63), 132 (11), 129 (53), 106 (100), 101 (27), 87 (10), 79 (13), 77 (12), 59 (18), 57 (92). IR (MeCN) ν/cm^{-1}: 3638, 3544, 3341, 2990, 2947, 1712, 1650, 1307, 1250, 1175, 1074, 900, 710.

N^2-Ethoxypropylene-2-(*N*-Boc-amino)-2-phenylacethydrazide (**3e**, Entries 9 and 10).

This compound was obtained as a white solid in 76% yield, mp 120-121 °C, R_f 0.55 (benzene-AcOEt, 1:5 v/v). (Calcd. Anal. for $C_{18}H_{27}N_3O_4$: C, 62.01; H, 7.72; N, 12.12. Found: C, 62.30; H, 7.77; N, 12.07%). UV λ_{max} (MeOH): 202 nm ($\varepsilon \cdot 10^{-3}$ 15.26 cm^{-1}M^{-1}), 231 (10.07). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 9.52, 14.07, 21.65, 28.17, 56.64, 61.67, 78.41, 127.10, 127.78, 128.23, 138.91, 155.03, 165.68, 168.75. MS (EI, 70 eV) *m/z* (%): 206 (10), 151 (13), 150 (65), 143 (62), 132 (11), 115 (28), 106 (100), 104 (17), 87 (10), 79 (15), 77 (12), 59 (15), 57 (95). IR (MeCN) ν/cm^{-1}: 3644, 3546, 3381, 2992, 2945, 1708, 1640, 1252,

1175, 1073, 900, 761, 705.

N^2-Ethoxybenzylidene-2-(*N*-Boc-amino)-2-phenylacethydrazide (**3f**, Entries 11 and 12).

This compound was obtained as a white solid in 89% yield, mp 134-135 °C, R_f 0.56 (benzene-AcOEt, 1:5 v/v). (Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.50; H, 6.80; N, 10.58. Found: C, 66.69; H, 6.84; N, 10.69%). UV λ_{max} (MeOH): 201 nm ($\varepsilon \cdot 10^{-3}$ 18.91cm^{-1}M^{-1}), 269 (11.60). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 15.01, 28.14, 56.48, 62.82, 78.47, 127.17, 127.37, 127.85, 128.15, 128.33, 128.64, 128.95, 138.57, 138.83, 155.10, 166.69, 171.25. MS (EI, 70 eV) *m/z* (%): 206 (12), 191 (40), 177 (21), 163 (15), 150 (51), 132 (10), 106 (100), 105 (78), 104 (51), 103 (22), 87 (11), 79 (23), 77 (62), 59 (15), 57 (79). IR (MeCN) ν/cm^{-1}: 3640, 3558, 3374, 3031, 2986, 1702, 1634, 1322, 1245, 1173, 1081, 1022, 895, 763, 724.

Cyclization of *N*-Boc protected N^2-ethoxymethylene phenylglycine hydrazides to *N*-Boc protected 2-(1-aminomethyl)-1,3,4-oxadiazoles (4a-d). The appropriate *N*-protected N^2-ethoxymethylene phenylglycine hydrazide (3c-f) (5 mmol) was dissolved in 10 mL of glacial AcOH. The mixture was kept on a water bath at 50 °C for about 4 hours (TLC). Then the solution was concentrated on a rotary evaporator. The crude products (4a-d) were subjected to the column chromatography (silica gel, eluent: benzene-AcOEt, 1:5 mixture) or were crystallized from benzene-hexane mixtures.

2-(1-*N*-Boc-amino-1-phenylmethyl)-1,3,4-oxadiazole (4a).[21]

This compound was obtained as a white solid in 75% yield, mp 113-115 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (9H, s, $(CH_3)_3$), 6.14 (1H, d, J = 8.1 Hz, CH), 7.32-7.45 (5H, m, Ph), 8.31 (1H, d, J = 8.1 Hz, NH), 9.20 (1H, s, H-C5). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 28.09, 50.44, 78.96, 127.56, 128.22, 128.55, 137.00, 154.77 (CO-O-*t*-Bu), 156.08 (C5), 165.74 (C2).

5-Methyl-2-(1-*N*-Boc-amino-1-phenylmethyl)-1,3,4-oxadiazole (**4b**).[21]

This compound was obtained as a white solid in 81% yield, mp 98-100 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (9H, s, $(CH_3)_3$), 2.44 (3H, s, CH_3-C5), 6.03 (1H, d, J = 8.1 Hz, CH), 7.32 -7.43 (5H, m, Ph), 8.25 (1H, d, J = 8,1 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.55, 28.19, 50.58, 79.00, 127.62, 128.25, 128.63, 137.21, 155.01 (CO-O-*t*-Bu), 164.25 (C5), 165.93 (C2).

5-Ethyl-2-(1-*N*-Boc-amino-1-phenylmethyl)-1,3,4-oxadiazole (**4c**).[21]

This compound was obtained as a white solid in 85% yield, mp 123-125 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.21 (3H, t, J = 8.1 Hz, CH_3-C5), 1.38 (9H, s, $(CH_3)_3$), 2.81 (2H, q, J = 8.1 Hz, CH_2-C5), 6.03 (1H, d, J = 8.1 Hz, CH), 7.31-7.41 (5H, m, Ph), 8.24 (1H, d, J = 8,1 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.45, 18.35, 28.19, 50.63, 78.99, 127.62, 128.24, 128.63, 137.22, 155.03 (CO-O-*t*-Bu), 165.82 (C2), 168.10 (C5).

2-(1-*N*-Boc-amino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**4d**).[21]

This compound was obtained as a white solid in 92% yield, mp 131-133 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (9H, s, $(CH_3)_3$), 6.19 (1H, d, J = 8.1 Hz, CH), 7.33-7.42 (3H, m, C2 - H-3', H-4', H-5'), 7.49 (2H, d, J = 6.9 Hz, C2 - H-2', H-6'), 7.55-7.62 (3H, m, C5 - H-3", H-4", H-5"), 7.95 (2H, d, J = 7.8 Hz, C5 - H-2", H-6"), 8.38 (1H, s, J = 8.1 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 28.10, 50.63, 79.03, 123.14, 126.48, 127.55, 128.25, 128.62, 129.45, 132.10, 137.06, 155.00 (CO-O-*t*-Bu), 164.33 (C5), 165.99 (C2). IR (MeCN) ν/cm^{-1}: 3644, 3516, 3362, 2980, 1723, 1648, 1560, 1241, 1165, 1024, 900, 782, 724.

Transformation of *N*-Boc protected N^2-ethoxymethylene phenylglycine hydrazides to *N*-Ac protected 2-(1-aminomethyl)-1,3,4-oxadiazoles (5a-d). The appropriate *N*-protected N^2-ethoxymethylene phenylglycine hydrazide (**3c-f**) (5 mmol) was dissolved in 10 mL of glacial AcOH. The mixture was kept under reflux for about 1-2 h (TLC). Then the solution was concentrated on a rotary evaporator. The crude products (**5a-d**) were crystallized from EtOH.

2-(1-*N*-Ac-amino-1-phenylmethyl)-1,3,4-oxadiazole (**5a**).[21]

This compound was obtained as a white solid in 94% yield, mp 120-121 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.95 (3H, s, CH_3), 6.40 (1H, d, J = 7.8 Hz, CH), 7.36-7.42 (5H, m, Ph), 9.18 (1H, d, J = 7.8 Hz, NH), 9.23 (1H, s, H-C5). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 22.29, 48.75, 127.59, 128.41, 128.79, 136.76, 154.85 (C5), 165.60 (C2), 169.21 ($COCH_3$).

5-Methyl-2-(1-*N*-Ac-amino-1-phenylmethyl)-1,3,4-oxadiazole (**5b**).[21]

This compound was obtained as a white solid in 95% yield, mp 112-113 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.90 (3H, s, CH_3), 2.47 (3H, s, CH_3-C5), 6.30 (1H, d, J = 8.1 Hz, CH), 7.33-7.40 (5H, m, Ph), 9.19 (1H, d, J = 8.1 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.54, 22.32, 48.72, 127.57, 128.33, 128.75, 136.92, 164.23 (C5), 165.71 (C2), 169.16 ($COCH_3$).

5-Ethyl-2-(1-*N*-Ac-amino-1-phenylmethyl)-1,3,4-oxadiazole (**5c**).[21]

This compound was obtained as a white solid in 95% yield, mp 89-91 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22 (3H, t, J = 7.5 Hz, CH_3-C5), 1.94 (3H, s, CH_3), 2.83 (2H, q, J = 7.5 Hz, CH_2-C5), 6.33 (1H, d, J = 8.1 Hz, CH), 7.37-7.41 (5H, m, Ph), 9.15 (1H, d, J = 8.1 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.34, 18.29, 22.29, 48.73, 127.52, 128.31, 128.74, 136.93, 165.59 (C2), 168.03 (C5), 169.09 ($COCH_3$).

2-(1-*N*-Ac-amino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**5d**).[21]

This compound was obtained as a white solid in 98% yield, mp 167-168 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.97 (3H, s, CH_3), 6.44 (1H, d, J= 8.1 Hz, CH), 7.34-7.41 (3H, m, C2 – H-3', H-4', H-5'), 7.48 (2H, d, J = 7.5 Hz, C2 - H-2', H-6'), 7.56-7.60 (3H, m, C5 – H-3", H-4", H-5"), 7.95 (2H, d, J = 7.8

Hz, C5 - H-2", H-6") , 9.29 (1H, d, J = 8.1 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 22.34, 48.96, 123.13, 126.57, 127.64, 128.39, 128.79, 129.47, 132.14, 136.81, 164.37 (C5), 165.93 (C2), 169.31 ($COCH_3$). IR (MeCN) ν/cm^{-1}: 3645, 3542, 3361, 3020, 1693, 1632, 1244, 1087, 966, 908.

Transformation of *N*-Boc protected 2-(1-aminomethyl)-1,3,4-oxadiazoles (4b, 4d) into their *N*-Ac protected counterparts (5b, **5d).** The appropriate 2-(1-*N*-Boc-amino-1-phenylmethyl)-1,3,4-oxadiazole (**4b**, **4d**) (3.5 mmol) was dissolved in 10 mL of glacial AcOH. The mixture was kept under reflux for about 1-2 h (TLC). Then the solution was concentrated on a rotary evaporator. The crude products (**5b**, **5d**) were subjected to the column chromatography (silica gel, eluent: MeOH-$CHCl_3$, 1:1 mixture) giving the pure *N*-Ac protected 1,3,4-oxadiazoles: **5b** (yield: 82%, mp 112-113° C), **5d** (yield: 95%, mp 166-168 °C).

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